Burden of disease of X-linked hypophosphatemia in Japanese and Korean patients: a cross-sectional survey

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Abstract. The burden of disease of X-linked hypophosphatemia (XLH) in East Asia is poorly understood. This was a cross-sectional study using an online questionnaire to evaluate health-related quality of life (HRQOL) and disease complications in Japanese and Korean patients with XLH. Adults with XLH and the caregivers of children <18 years of age with XLH in Japan and Korea were surveyed. Respondents disclosed demographic data, family history, diagnostic history, medical history, surgical history, disease-specific clinical symptoms, treatment, medications, and use of ancillary equipment. Patient-reported outcomes (PROs; the Western Ontario and McMaster Universities Osteoarthritis Index, the brief pain inventory, and the 36-item short form health survey version 2) were used to assess pain, disability, and HRQOL in adults. Of those surveyed, all 14 children (100%) and 30/32 adults (93.8%) were receiving treatment for XLH. However, despite oral phosphate and active vitamin D use, short stature, gait abnormalities, dental conditions, and decreased physical function were reported. Stapling of the growth plates was reported in 14.3% of children but no adults. Adult patients reported high rates of bone pain (59.4%) and joint pain (65.6%). Caregivers of children with XLH also reported the occurrence of bone pain (35.7%) and joint pain (35.7%). Many adult patients had a history of impaired renal function (9.5%), nephrocalcinosis (15.6%), hyperparathyroidism (15.6%), and parathyroidectomy (6.3%), all of which are associated with conventional XLH treatments. These data show that patients (both pediatric and adult) continue to have symptoms such as pain, disability, and various complications despite receiving conventional therapies.

Key words: X-linked hypophosphatemia, Burden of disease, Survey, Health-related quality of life, Bone pain

X-LINKED HYPOPHOSPHATEMIA (XLH) is a rare, chronic, serious, and debilitating genetic disorder estimated to affect approximately one in 20,000 to 60,000 people [1-3]. XLH results from mutation of the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), which causes excessive secretion of fibroblast growth factor 23 (FGF23) [4-6]. FGF23 is a key hormone in the process of maintaining phosphate homeostasis [7], and an excess of FGF23 activity causes renal phosphate wasting, chronic hypophosphatemia, and skeletal manifestations [8-10]. In children with ongoing bone growth, chronic hypophosphatemia causes rickets, which manifests as leg deformity, decreased growth, and bone and joint pain [11-14]. Unresolved symptoms from childhood may manifest in adults, which include lower limb deformity and short stature. In addition, continued hypophosphatemia in adults with stopped bone growth results in osteomalacia and its complications, such as pseudo fractures and fractures. Patients may also present with osteoarthritis and enthesisopathy. Further, these manifestations can cause pain [4, 15, 16]. The ensuing musculoskeletal symptoms, such as pain and stiffness, impair physical function and affect quality of life [15, 17, 18]. Patients
also present with dental problems, such as periodontitis and dental abscess, due to defects in dentin and enamel [19].

Since the 1980s, the conventional treatment for XLH has been a combination of active vitamin D and oral phosphate [20, 21], with the goal of improving bone mineralization, minimizing skeletal deformity, and maximizing growth potential. However, it is difficult to administer sufficient oral phosphate due to iatrogenic risks (such as nephrocalcinosis, hypercalcuiaria, and secondary and/or tertiary hyperparathyroidism) [6, 13, 20, 22] and clinical outcomes can vary widely [13, 23].

Burosumab, a fully human monoclonal antibody targeted against FGF23 [24] became available in Japan in December 2019 for the treatment of FGF23-related hypophosphatemic rickets and osteomalacia [25] and was approved in Korea in September 2020. In recent clinical trials in pediatric and adult patients with XLH, burosumab treatment has demonstrated efficacy (by restoring normal serum phosphate levels and increasing the production of 1,25(OH)2D, decreasing the severity of rickets/osteomalacia, and improving markers of bone formation and resorption) with minimal safety concerns [26-30].

As XLH is a rare disease, there has been a paucity of information regarding the burden placed on patients and their families, particularly with regard to health-related quality of life (HRQOL). The XLH Burden of Disease Study, a non-interventional, global, online survey of a large cohort of 90 children and 232 adults with XLH, was previously published [31]. However, this study used questionnaires in English, French, Spanish, Portuguese, and German; no Japanese or Korean language surveys were conducted, meaning that East Asian data are still lacking. Because the medical environment (including diagnosis, drug availability/usage, and costs) and socioeconomic environment (including HRQOL standards and productivity) can vary by country and geographic region, the collection of data from East Asian patients is key to understanding the challenges of living with XLH in Japan and Korea. Thus, we conducted a survey to evaluate the clinical presentation, patient-reported symptoms, and impact of the disease on function and HRQOL in Japanese and Korean patients to understand the disease burden in this region.

Patients and Methods

Study design and setting
This survey was conducted to evaluate the clinical presentation, patient-reported symptoms, and impact of XLH in both children and adults in Japan and Korea. Full details of the study methodology have been published [31]. In brief, the XLH Burden of Disease Survey was a cross-sectional study using an online questionnaire designed in collaboration with The XLH Network Inc., a patient advocacy group, and a team of researchers employed by Ultragenyx Pharmaceutical Inc. or Kyowa Kirin Co., Ltd. or affiliated with these companies. The survey period was from August 2017 to December 2019. The questionnaire required about 30 minutes to complete, and participants were requested to complete the survey in one sitting.

The questions and assessments included in the survey were developed based on regulatory recommendations, a qualitative interview with a patient with XLH or caregiver (parents or a legal representative) [32], and literature on HRQOL in conditions similar to XLH, such as osteoarthritis [33-36]. There were two versions of the questionnaire: one for adult XLH patients and one for children <18 years of age with XLH, which was completed by the caregiver. The data directly reflected the responses received and were not verified with medical records. No identifiers were collected to ensure anonymity.

Participants
This was a non-interventional online survey of children (via their caregivers) and adults with XLH in Japan and Korea. Adult participants with XLH and caregivers of children with XLH were recruited through referrals from clinicians with a research interest in XLH or personal clinical management experience with XLH.

Survey respondents were adults aged ≥18 years of age. For pediatric patients, a legal representative (generally a parent or other caregiver) completed the questionnaire. Caregivers were instructed to complete one survey for each individual child in their care with a diagnosis of XLH; thus, if a caregiver had multiple children with XLH, they answered the survey separately for each child.

Respondents were asked to confirm the diagnosis of XLH received for themselves or their child and whether they had received genetic confirmation of a PHEX mutation; however, the diagnosis was not verified with medical records.

The protocol, consent form, and participant materials for the survey were reviewed and approved by the New England Institutional Review Board (USA) (approval number: 120160148). Each adult patient and the legal representatives of pediatric patients provided informed consent for publication of data. The XLH Burden of Disease Survey included an electronic consent form. Study participants were guided by a web portal that provided the online consent forms that required completion before accessing the survey.
Survey questions
The questionnaires for all patients, written in Japanese or Korean, included items on demographic data, family history, diagnostic history, medical history, surgical history, disease-specific clinical symptoms, treatment, medications, and use of assistive devices.

Patient-reported outcomes (PROs) were used to assess pain, disability, and HRQOL in adults. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [37] was used to assess pain, stiffness, and physical function. WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68); a higher score correlates with poorer function. WOMAC index scores were normalized to a 0–100 metric representing the percent of a maximum score, as described in the WOMAC user guide (version XI) [38]. The brief pain inventory (BPI) [39] was used to assess pain severity and interference with daily life. Pain intensity was measured in four categories (worst, least, average, and current), and pain interference in seven categories (mood, work, general activity, walking, relationships, enjoyment of life, and sleep); each category was rated on a scale from 0–10, with a higher score indicating either higher pain severity or increased impact on daily life. The 36-item short form health survey version 2 (SF-36v2) [40] was used to assess HRQOL. The SF-36v2 consists of eight domains (vitality, physical functioning, bodily pain, general health, role physical, role emotional, social functioning, and mental health) from which component summary scores reflecting physical and mental health are derived; lower scores indicate higher levels of disability. SF-36v2 scores were transformed using norm-based scoring, which standardized the values with respect to US population norms, which have a mean (standard deviation [SD]) of 50 (10). This procedure was in line with that used in the global study [31], and allowed for inter-country comparisons. Minimally important differences (MIDs) and the resulting 50–MID scores in each domain (T-score points) were as follows: physical component summary, 2 and 48; mental component summary, 3 and 47; physical functioning, 3 and 47; role physical, 3 and 47; bodily pain, 3 and 47; general health, 2 and 48; vitality, 2 and 48; social functioning, 3 and 47; role emotional, 4 and 46; and mental health, 3 and 47 [41].

Statistical methods
Demographic data were assessed using frequency distributions and disease characteristics using summary measures. Height was evaluated using the standard deviation score (SDS) for each age [42]. All PRO data were reported as continuous variables, using mean (SD or standard error). Missing data were handled according to the method recommended for each scale by its developer. All analyses were conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Patient and public involvement
The XLH Network Inc. was involved in the preparation of questionnaires. There was no involvement of patients or the public in the plans to disseminate the study results.

Results
Demographics and family history
The study respondents included 32 adults with XLH and 14 caregivers of children with XLH. Five children (35.7%) were Japanese, and nine (64.3%) were Korean; 27 adults (84.4%) were Japanese, and five (15.6%) were Korean. Baseline demographic and clinical data are shown in Table 1. Among the children, 9/14 (64.3%) were female, and among the adults, 18/32 (56.3%) were female. The mean (SD) age of the children was 6.8 (3.7) years (range 3–17) and that of the adults was 40.2 (13.8) years (range 18–71). The mean (SD) age of the children at symptom onset was 1.5 (1.5) years (range 0–5) and that of the adults was 7.2 (15.2) years (range 0–54). In total, 12/14 children (85.7%) and 21/32 adults (65.6%) self-reported PHEX mutations as confirmed by genetic diagnosis.

Current treatment
At the time of the survey, all 14 children (100%) and 30/32 adults (93.8%) were receiving treatment for XLH (Table 1). The majority of both children and adults were receiving oral phosphate (12/14 [85.7%] and 20/32 [62.5%], respectively) and/or active vitamin D (10/14 [71.4%] and 24/32 [75.0%], respectively).

Overall, three children and nine adults had participated in a clinical trial of burosumab; of these, one child (7.1%) and four adults (12.5%) were receiving burosumab at the time the survey was conducted.

Clinical characteristics and surgical history
The mean (SD) SDS of adult height was –2.39 (1.9) in females and –2.68 (2.1) in males. Effects on growth are shown in Fig. 1a. Overall, 9/14 (64.3%) children and 15/32 (46.9%) adults reported short stature. In many patients, a curvature of the long bones was observed. Respectively, knock-knees, bowing of the legs at the femur, and bowing of the legs at the tibia/fibula were reported in 4/14 (28.6%), 5/14 (35.7%), and 8/14 (57.1%) children, and in 6/32 (18.8%), 13/32 (40.6%), and 15/32 (46.9%) adults.
Table 1  Demographic and clinical characteristics of the study population

|                          | Children     | Adults      |
|--------------------------|--------------|-------------|
|                          | N = 14       | N = 32      |
| Age (years), mean (SD)   | 6.8 (3.7)    | 40.2 (13.8) |
| Range                    | 3–17         | 18–71       |
| Female, n (%)            | 9 (64.3)     | 18 (56.3)   |
| Country, n (%)           |              |             |
| Japan                    | 5 (35.7)     | 27 (84.4)   |
| Korea                    | 9 (64.3)     | 5 (15.6)    |
| Age at symptom onset (years), mean (SD) | 1.5 (1.5)     | 7.2 (15.2)   |
| Range                    | 0–5          | 0–54        |
| Age at XLH diagnosis (years), mean (SD) | 1.9 (1.8)    | 12.3 (20.5) |
| Range                    | 0–6          | 0–70        |
| Self-reported PHEX mutation, n (%) | 12 (85.7)  | 21 (65.6)   |
| Currently receiving treatment for XLH, n (%) | 14 (100)   | 30 (93.8)   |
| Oral phosphate           | 12 (85.7)    | 20 (62.5)   |
| Active vitamin D         | 10 (71.4)    | 24 (75.0)   |
| Burosumab                | 1 (7.1)      | 4 (12.5)    |
| Previous participant in a clinical trial of burosumab, n (%) | 3 (21.4)  | 9 (28.1)    |

PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome; SD, standard deviation; XLH, X-linked hypophosphatemia.

Fig. 1  Health of patients with X-linked hypophosphatemia. a: Growth and stature. b: Dental complications. c: Other complications.
The most common surgical procedure reported was stapling of the growth plates (2/14 [14.3%]) in children and osteotomy (11/32 [34.4%]) in adults. In addition, 1/14 (7.1%) children and 2/32 (6.3%) adults had received skull surgery (either craniotomy or craniectomy).

Lower limb fractures in adults (history of either fracture or pseudo fracture) are described in Table 2. As non-traumatic fractures are uncommon in children, a history of fracture was not assessed in the pediatric survey. In total, 11/32 (34.4%) adults had experienced a fracture, of which the most common location was the femur (8/32 [25.0%]), with a mean (SD) age at femur fracture of 27.2 (11.6) years. Most patients had experienced only one fracture, but one patient had experienced two fractures, and another patient had five or more fractures. Common complications due to progressive XLH include osteophytes, enthesopathy, and spinal stenosis; these conditions were reported by 6/32 (18.8%), 2/32 (6.3%), and 2/32 (6.3%) adult participants, respectively. Dental complications are summarized in Fig. 1b. The most frequent dental complication was excessive cavities (4/14 [28.6%]) in children and osteotomy (11/32 [34.4%]) in adults. In addition, 1/14 (7.1%) children and 2/32 (6.3%) adults had received skull surgery (either craniotomy or craniectomy).

### Pain, stiffness, and functional limitations

As shown in Table 3, most patients with XLH reported bone pain (5/14 [35.7%] children and 19/32 [59.4%] adults), joint pain (5/14 [35.7%] children and 21/32 [65.6%] adults), or stiffness (12/32 [37.5%] adults). Muscle pain was reported in 4/14 (28.6%) children and 15/32 (46.9%) adults. The proportion of adults taking analgesics for pain at least once per week was 5/32 (15.6%).

In adult patients, mean BPI pain severity, pain interference, and worst pain (pain at its worst in the past 24 hours) scores were 2.9, 3.1, and 4.1, respectively (Fig. 2a), indicating moderate pain interference with daily functions in these patients. In support of this data, joint stiffness or a restricted range of motion was reported by 4/14 (28.6%) children and 21/32 (65.6%) adults. In addition, osteoarthritis, which is associated with the occurrence of joint pain and stiffness, was reported by 8/32 (25.0%) adults.

The average WOMAC stiffness domain score in adult patients with XLH was 30.9, and the physical function domain score was 25.1 (Fig. 2b). Regarding clinical symptoms and medical history influencing mobility, delayed walking was reported in 3/14 (21.4%) children, an unusual gait or way of walking/running in 8/14 (57.1%) children and 19/32 (59.4%) adults, muscular weakness in 3/14 (21.4%) children and 17/32 (53.1%) adults, and use of a walking device in 8/32 (25.0%) adults.

### HRQOL

The mean (SD) SF-36v2 physical component summary score was 41.2 (9); based on the standard normative value of 50, the physical component summary score was below the 50–MID value of 48 for this domain (Fig. 2c). The physical functioning, role physical, bodily pain, and general health subscale scores, which contributed most to the calculation of the physical component summary score, also showed impairment. Particularly, the general health score was 37.4 (9.3), which was below the norm of 50–1SD. The mean mental component summary score was 45.3 (13.4); based on the normative score, this was below the 50–MID of 47 for this domain. The

### Table 2  Fracture history in adults with XLH

| Location          | n (%) | Number of fractures, n | Mean (SD) age at first fracture, years |
|-------------------|-------|------------------------|--------------------------------------|
| All               | 11 (34.4) | — — — — — | —                                    |
| Femur (thigh)    | 8 (25.0)  | 7 0 0 0 1 | 27.2 (11.6) |
| Feet              | 3 (9.4)   | 2 1 0 0 0 | 29.7 (21.4) |

SD, standard deviation; XLH, X-linked hypophosphatemia.

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Table 3  Bone and joint pain in patients with XLH

| Location, n (%)                  | Bone pain | Joint pain | Joint stiffness |
|----------------------------------|-----------|------------|-----------------|
|                                  | Children  | Adults     | Children        | Adults     | Children | Adults             |
| Any                              | 5 (35.7)  | 19 (59.4)  | 5 (35.7)        | 21 (65.6) | N/A       | 12 (37.5)          |
| Any upper extremity              | 1 (7.1)   | 6 (18.8)   | 1 (7.1)         | 10 (31.3) | N/A       | 6 (18.8)           |
| Any lower extremity              | 5 (35.7)  | 18 (56.3)  | 5 (35.7)        | 21 (65.6) | N/A       | 12 (37.5)          |
| Back                             | 0 (0)     | 7 (21.9)   | 0 (0)           | 12 (37.5) | N/A       | 6 (18.8)           |
| Hips                             | 0 (0)     | 4 (12.5)   | 0 (0)           | 7 (21.9)  | N/A       | 2 (6.3)            |
| Upper leg (thigh)                | 1 (7.1)   | 5 (15.6)   | N/A             | N/A       | N/A       | N/A                |
| Knee                             | 4 (28.6)  | 7 (21.9)   | 5 (35.7)        | 16 (50.0) | N/A       | 8 (25.0)           |
| Lower leg (shin)                 | 1 (7.1)   | 3 (9.4)    | N/A             | N/A       | N/A       | N/A                |
| Ankle                            | 4 (28.6)  | 7 (21.9)   | 4 (28.6)        | 9 (28.1)  | N/A       | 6 (18.8)           |
| Feet                             | 2 (14.3)  | 7 (21.9)   | 2 (14.3)        | 9 (28.1)  | N/A       | 2 (6.3)            |
| Toes                             | 0 (0)     | 3 (9.4)    | 0 (0)           | 1 (3.1)   | N/A       | 0 (0)              |

N/A, not applicable; XLH, X-linked hypophosphatemia.

Fig. 2  Patient-reported outcomes in adult patients with XLH. a: BPI. b: WOMAC. c: SF-36v2. Data are means and standard errors. The norm score, and the 50–MID for each domain, are shown. BPI, brief pain inventory; MID, minimally important difference; SF-36v2, 36-item short form health survey version 2; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; XLH, X-linked hypophosphatemia.
vitality, social functioning, role emotional, and mental health subscale scores, which contributed most to the mental component summary score calculation, were all below the 50–MID value.

In the adult survey, participants were asked to respond to the question, “If you had to spend the rest of your life with this condition as it is right now, how would you feel about it?”. The results were “very dissatisfied” in 15/32 (46.9%) patients, “moderately dissatisfied” in 6/32 (18.8%), “neutral” in 10/32 (31.3%), “moderately satisfied” in 1/32 (3.1%), and “very satisfied” in 0/32 (0%).

**Discussion**

Patients with XLH are affected by various musculoskeletal problems throughout the course of their lifetime [4, 45]. Despite treatment with conventional therapy, many patients with XLH experience disability [13, 23]. Data on the burden of disease, particularly in East Asian patients, are lacking, so this survey was intended to elucidate that burden via the evaluation of the clinical presentation, patient-reported symptoms, and impact of the disease on function and HRQOL in Japanese and Korean patients with XLH.

The patients’ age (3–71 years) and their age at symptom onset (0–54 years) confirm the lifelong burden of disease. Although the adults participating in our analysis reported a later onset of symptoms and a later age at diagnosis compared with the responses submitted for children, this is likely due to a lack of information and awareness of XLH in earlier decades or to memory errors in adults, who have had their initial symptoms for a longer period of time.

Most patients in this survey were being actively treated for XLH, but short stature, gait abnormality, dental conditions, and impaired physical function were reported despite the use of oral phosphate formulations and active vitamin D. Adult patients reported clinical manifestations resulting from ongoing osteomalacia (bone pain, pseudofractures and fractures), arthralgia, joint stiffness, and osteoarthritis, in addition to unresolved complications from childhood (short stature and leg deformations). Dental complications were also common in patients of all ages with XLH, indicating the need for careful monitoring by a dental practitioner. In particular, root canal surgery and dental implant failure are serious conditions for adults, which warrant further research in the future. All of these results were in line with those reported by American and European patients in the previous XLH Burden of Disease article [31] and in other prior XLH publications [46–51].

In a previous analysis of Japanese adults with XLH, the final height SDS for conventionally treated patients was –1.7 [52], whereas, in this study, it was –2.39 for females and –2.68 for males. Because our study included patients from Korea and Japan, the difference in height SDS between studies may be due to the disparate patient populations. It is also possible that the difference may be related to the dose or duration of conventional therapy; however, as the current study was questionnaire-based and patient-reported, it was not possible to obtain accurate information on dose and duration of treatment. Thus, additional investigation is required to ascertain the relationship between conventional treatment and final height.

In terms of participants’ surgical history, stapling of the growth plates was reported in 14.3% of children but no adults. As this is a recently developed surgical procedure performed before adulthood [53], it is not surprising that no procedures were reported by adult XLH patients; we anticipate that studies in future decades will show a more even distribution as the current XLH pediatric population reaches maturity. Conversely, we found that while 34.4% of adults had undergone osteotomy, no children had undergone this procedure. These differences in surgical history between adults and children may indicate that the main surgical procedure for XLH has shifted from osteotomy to stapling of the growth plates with ongoing bone growth.

Adults with XLH commonly reported fractures [43, 54, 55], particularly pseudofractures due to osteomalacia [56]. However, although patients in our survey did report fractures, the occurrence rates appeared to be lower than those reported by American and European patients in the global XLH Burden of Disease Study [31]. The reasons for this are unclear, but it is important to note that the XLH Burden of Disease Survey was unable to definitively distinguish between common fractures and specific osteomalacia-associated pseudofractures, and that patients may not be able to reliably discriminate between types of fracture, which may have confounded these data. It is also worth noting that rates of fracture/pseudofracture vary widely from 18%–54%, in other studies of XLH patients [51], which likely reflects different methodology in eliciting and recording information.

One of the other most common clinical manifestations of osteomalacia is generalized or localized bone pain [23, 57]. Our data did show high rates of bone pain in adult patients, and all of the PROs in adult patients indicated that adults experience pain, stiffness, and functional limitations. Moreover, caregivers of children with XLH also reported the occurrence of bone pain and joint pain in the children. Bone and joint pain have also been reported in large proportions (up to 100%) of patients in prior XLH studies [51]. Notably, adult patients participating in our survey reported SF-36v2
physical component summary and subscale scores that were comparable with those reported by patients with other chronic pain conditions such as lower back pain, osteoarthritis, and axial spondyloarthritis [17, 44, 58], indicating a substantial disease burden.

In this East Asian XLH population, fewer adults with XLH reported bone and joint pain and used analgesics compared with patients taking part in the global survey [31] and other prior analyses of XLH patients [51]. The reasons for this difference are unclear, although it may be due to the higher rates of current oral phosphate and active vitamin D treatment in East Asian adults (62.5% and 75.0%, respectively) compared with adults from other regions (49.1% and 64.2%, respectively [31]). However, it must be noted that these treatments are associated with adverse events [4, 6, 13], and many East Asian patients had a history of impaired renal function, nephrocalcinosis, hyperparathyroidism, and parathyroidectomy. Thus, regular renal ultrasonography and monitoring of renal function and parathyroid hormone are warranted in patients receiving conventional XLH treatments.

Although burosumab has demonstrated acceptable efficacy and safety for the treatment of XLH [26-29], it was not available in Japan until December 2019 (which corresponded with the end of the survey period), and it was not approved in Korea at the time of the survey. Therefore, it is not surprising that only five respondents reported that they were currently being treated with burosumab during the survey period. While 12 respondents (26%) reported that they had participated in a previous clinical study with burosumab, the limited available data do not allow us to make any inferences about the effect of burosumab on the burden of XLH. Further studies to prospectively examine the impact of burosumab on HRQOL are warranted.

The limitations of this survey methodology have been reported [31]. These limitations include selection bias (because many patients were referred by a physician and were currently receiving treatment); thus, our study may not reflect the status of the wider population of East Asian patients with XLH. Moreover, the methodology used to analyze the data according to global standards, by adjusting some PRO scores using the US norms, is consistent with the prior global study [31], but may not accurately reflect the true situation of Japanese and Korean patients. As with any analysis that relies on self-reporting by patients and is not confirmed with medical records, we are limited by the accuracy of the responses received, and the lack of precise information on symptoms, treatments, and outcomes precludes the formulation of definitive conclusions. Although patients were able to select checkboxes for specific complications and symptoms, these were dependent on patient knowledge and recollection, and there was no medical confirmation of the accuracy of each selection. For example, renal impairment or hyperparathyroidism, which were defined by a physician’s diagnosis, might not have been reported correctly if the patient did not recognize these medical terms. Furthermore, the subjective nature of the data means that the type and severity of morbidity as reported by the patients might not be accurate. Although PHEX mutational status was not confirmed in all patients, only individuals who had been clinically diagnosed with XLH by an experienced physician were referred for study participation. Thus, all patients were considered to have a definitive diagnosis of XLH based on family history, comparatively high levels of FGF23, and clinical manifestations, with or without confirmation by genetic testing. The sample size was small; however, as XLH is a rare condition, we consider our sample size to represent a sizeable proportion of the population. Despite these limitations, this survey has provided important information on the burden of XLH due to joint or bone pain or stiffness, difficulties in daily life, and HRQOL, which were previously unknown in Japanese and Korean patients with XLH. When added to the data from the prior global study and the literature, our results help to further elucidate the worldwide burden of XLH.

Conclusions

This survey was able to clarify the burden of disease from the viewpoint of East Asian patients with XLH. The data revealed that many patients (both pediatric and adult) continue to have symptoms such as pain, disability, and various complications despite receiving conventional therapies such as oral phosphate and active vitamin D.

Declarations

Ethics approval and consent to participate

The protocol, consent form, and participant materials for the survey were reviewed and approved by the New England Institutional Review Board (USA) (approval number: 120160148). Each patient or their caregivers (parents or a legal representative) provided informed consent for publication of data. The XLH Burden of Disease Survey included an electronic consent form, and study participants were guided by a web portal that provided the online consent forms that required completion before accessing the survey.

Availability of data and materials

The dataset of individual deidentified participant data
supporting the conclusions of this study and the protocol will be available for at least 12 months after publication to researchers providing a methodologically sound proposal that is in accordance with Ultragenyx’s data-sharing policy. To gain access, data requestors will need to sign a data access and use agreement. Data will be shared via a secured portal.

**Competing interests**

NI has served as a clinical investigator for one or more studies, including this trial, sponsored by Kyowa Kirin Co., Ltd. and by Ultragenyx Pharmaceutical Inc. in partnership with Kyowa Kirin International PLC; and has received research grants from Kyowa Kirin Co., Ltd. and Ultragenyx Pharmaceutical Inc. HGK has received a research grant from Kyowa Kirin Co., Ltd. for the submitted work; and grants and personal fees from Alexion Pharmaceuticals Inc. and Handok Inc. outside the submitted work. YN is an employee of Kyowa Kirin Co., Ltd. AE is an employee of Ultragenyx Pharmaceutical Inc. AS is an employee of Ultragenyx Pharmaceutical Inc and holds shares in the company. HIC serves as a clinical trial investigator for Ultragenyx Pharmaceutical Inc.

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**Authors’ contributions**

NI, HGK, YN, AE, AS, and HIC were responsible for the study design. AE and AS were responsible for study conduct, and for data collection and analysis. NI, HGK, YN, and HIC were responsible for data interpretation. NI and YN wrote the manuscript, and HGK, AE, AS, and HIC critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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