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Terence Burgo, Brian Andrich Pollo

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Skeletal Survey of a Filipino Teenage Female with Ohdo syndrome: Case Report

Terence Aaron L. Burgo[1,*] (ORCID: https://orcid.org/0009-0002-9987-253X), Brian Andrich L. Pollo[2] (ORCID: https://orcid.org/0000-0001-6528-1550)

[1]Manila Doctors Hospital

[2]Biomedical Innovations Research for Translational Health Science (BIRTHS) Laboratory, Department of Biochemistry and Molecular Biology, College of Medicine, University of the Philippines Manila

*Address correspondence to this author at the Biomedical Innovations Research for Translational Health Science (BIRTHS) Laboratory, Department of Biochemistry and Molecular Biology, College of Medicine, University of the Philippines Manila, Medical Annex Building (Salcedo Hall), 547 Pedro Gil Street, Ermita, Manila 1000, Philippines; Tel/Fax: +63-2-8526-4197; E-mail: terenceburgo@gmail.com

ABSTRACT

Introduction: Ohdo syndrome is a rare congenital disorder occurring in less than 1 in a million individuals, characterized by intellectual disability, craniofacial abnormalities, as well as appendicular abnormalities. Caused by pathogenic variants in *KAT6B*, the orphan syndrome suffers from a paucity of reported cases, with less than 30 cases reported worldwide. Here, we present detailed skeletal survey findings of a genetically confirmed case of Ohdo syndrome, Say-Barber-Biesecker-Young-Simpson (SBBYS) variant (OMIM: 60376). To the best of our knowledge, this is the first reported case of Ohdo syndrome in the Philippines.

Case Presentation: A 16-year-old Filipino female who presented with intellectual disability was referred for diagnostic work-up. Physical examination revealed blepharophimosis, ptosis, rounded nose tip, broad nasal bridge, and widely spaced teeth, consistent with craniofacial findings in Ohdo syndrome. Skeletal survey demonstrated micrognathia, scoliosis, negative ulnar variance, bilateral shortened distal phalanges of the 2nd digits of the hand, and bilateral long first metatarsal bones of the feet.

Conclusion: This case illustrates the value of skeletal surveys in revealing structural abnormalities in Ohdo syndrome. Skeletal surveys may be used for documenting the extent and the severity of the phenotype. Further, such studies may inform referrals (*e.g.,* orthopedic or rehabilitation medicine) and surveillance (*e.g.,* for scoliosis).

Keywords: Intellectual disability, Craniofacial abnormalities, Ohdo syndrome, Case Report, Radiography

INTRODUCTION

Ohdo syndrome is rare congenital condition which comprises a heterogeneous group of disorders characterized by intellectual disability and typical facial features, including blepharophimosis. First described in the 1980s, the syndrome has since been subdivided into several clinical variants based on phenotypic and genotypic features, one of which is the Say-Barber-Biesecker-Young-Simpson (SBBYS) type [1–4].

The Say-Barber-Biesecker-Young-Simpson (SBBYS) variant of Ohdo (OMIM: 603736) is caused by heterozygous pathogenic variants in the *KAT6B* gene, which encodes a histone acetyltransferase involved in transcriptional regulation during embryonic development. Males with the SBBYS variant of Ohdo syndrome typically have cryptorchidism, while females with this condition have normal genitalia. Affected individuals also have joint stiffness involving the hips, knees, and ankles that can impair movement. Although joints in the lower body are stiff, joints in the arms and upper body may be unusually lax. Many people with this condition have long thumbs and first toes. The SBBYS variant of Ohdo syndrome is also associated with delayed development and intellectual disability, which are often severe. Many affected infants have weak muscle tone hypotonia that leads to breathing and feeding difficulties. The SBBYS variant of Ohdo syndrome is characterized by a mask-like, non-expressive face. Additionally, affected individuals may have distinctive facial features such as prominent cheeks, a broad nasal bridge or a nose with a rounded tip, a narrowing of the blepharophimosis, ptosis, and abnormalities of the lacrimal glands. About one-third of affected individuals are born with cleft palate. The SBBYS variant of Ohdo syndrome can also be associated with heart defects and dental problems.

Despite the increasing availability of genomic testing, Ohdo syndrome remains underdiagnosed due to its rarity and clinical overlap with other syndromic forms of intellectual disability and craniofacial dysmorphism. Fewer than 30 cases of the SBBYS variant have been documented in literature, with none reported for the Philippines. Descriptions from up-to-date radiologic studies of high resolution, particularly of complete skeletal surveys, remain sparse, limiting the ability to define syndrome-specific imaging patterns that may support early diagnosis.

In this report, we present a genetically confirmed case of Ohdo syndrome, SBBYS variant, in a Filipino patient. We provide a detailed account of the skeletal survey findings, aiming to contribute to the growing body of knowledge surrounding this ultra-rare condition.

CASE PRESENTATION

This is a case of a 16-year-old female who presented with intellectual disability and multiple syndromic features. The patient was born full-term to a then G3P3 35-year-old mother via normal spontaneous vaginal delivery. The patient had poor cry and was hypotonic at birth. Birthweight is approximately 2500 grams. Her parents are unrelated. Marked blepharophimosis and ptosis were noticeable postnatally. The mother denied taking drugs, smoking, alcohol nor history of any ailments during pregnancy. Her two other siblings are normal. No known similar syndromes afflicted known members of her family. She began to walk at the age of 2. She did not learn how to speak even a single word but is able to respond to name calling and commands. She was enrolled at a special school but was unable to cope and eventually dropped out due to uncontrollable tantrums and uncooperativeness. They consulted a pediatric geneticist and was advised psychological exam to assess intellectual capacity which revealed an IQ below 70 and was then diagnosed with intellectual disability. Menarche is at 14 years of age. Secondary sexual characteristics started to appear at the age of 14 as well and has not yet reached the adult stage currently.

Still perplexed by her daughter's condition, the mother, who is an overseas Filipino worker in Cyprus, researched about the syndrome and connected with various organizations who help individuals with rare conditions. She was then advised to have genetic tests. Hence, whole exome sequencing was done, revealing mutations in *KAT6B*. These mutations are the cause of Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome. To further investigate other associated abnormalities, multiple diagnostic exams were suggested. Laboratory examinations were done such as complete blood count, urinalysis and thyroid function test which yielded normal results. Referral to a Pediatric Radiologist was contemplated hence consult at our Department of Radiology.

On physical examination **Figure 1**, stooped posture and lax joints were noted. The patient had blepharophimosis and ptosis, intermittent nystagmus, broad nasal bridge, rounded nose tip, and micrognathia. Hand examination findings include relatively long thumbs, single palmar crease, atrophic hypothenar and thenar muscles, and stiff phalangeal joints. The first phalanges of the feet were large. Other significant systemic physical examination findings include grade 3/4 holosystolic murmur over the left sternal region and widely spaced teeth.

Skeletal survey was performed according to institutional guidelines, including views of the skull, thoracolumbar spine, upper and lower extremities, and hands and feet. Skull demonstrated micrognathia (**Figure 2**). For the thoracolumbar spine AP, scoliosis was noted, and the ribs,

clavicles and shoulder girdles were intact. The distal ulna is proximally located with respect to the radius (negative ulnar variance). The distal phalanges of both 2nd digits of the hands are shortened with flexion of their distal interphalangeal joints (**Figure 3**). There is hyperextension of both 2nd and 3rd proximal interphalangeal joints with compensatory flexion of their distal interphalangeal joints. Bone aging of the left hand and wrist is comparable with that of a 17-year-old female based on the Greulich and Pyle Method. The knee radiograph revealed normal patellae. For the feet, the patient had bilateral long 1st metatarsal bones and bilateral hallux valgi deformity.

The above findings are the majority of the skeletal abnormalities that can be found in Ohdo syndrome. The normal patellae points against a diagnosis of a separate entity still caused by mutations in *KAT6B* called Genitopatellar syndrome. This syndrome is characterized by absent patellae, genital abnormalities and intellectual disability. MRI of the brain and dental panoramic radiograph were also suggested but were not performed due to the uncooperative behavior of the patient. The patient was then lost to follow-up. No other subsequent diagnostic assessment and therapeutic interventions were noted.

DISCUSSION

Ohdo syndrome was first described by Shozo Ohdo, a Japanese Geneticist, in 1986. Together with his colleagues, they reported two sisters with intellectual disability, congenital heart disease, blepharophimosis, blepharoptosis, and hypoplastic teeth. The mode of inheritance is compatible with autosomal recessive inheritance, autosomal dominant inheritance with low penetrance, and multifactorial inheritance [1].

In 1991, Burhan Say and Nancy Barber, geneticists from Children's Medical Center in Oklahoma together with Leslie Biesecker from University of Michigan Medical Center also presented another case of mental retardation with blepharophimosis. The patients reported by Say and Barber had myopia and horizontal nystagmus, depressed nasal bridge, mid-facial hypoplasia, low set round ears and small oral cavity. Other findings include hyperextensible joints, clinodactyly of the fifth fingers bilaterally and hypoplastic thenar eminences. Additionally, there was generalized muscular hypotonia and dislocated right patella. Psychometric evaluation showed developmental lag of over 50% in all areas. The patient presented by Biesecker has a syndrome consisting of blepharophimosis, simple ears, hypoplastic teeth, developmental delay, and hypotonia. They concluded that this is distinct entity and should be considered among the differential diagnoses in patients with mental retardation, blepharophimosis and dental abnormalities [3,4]. Additionally, in 1987, Young and Simpson from the Department of Child

Health, Leicester Royal Infirmary, described a girl with congenital heart defects, hypothyroidism, mental retardation, and facial dysmorphism, including blepharophimosis [2].

In 2006, Verloes et al. described 11 patients from 8 families with a blepharophimosis-mental retardation syndrome (BMRS) phenotype and suggested a classification of BMRS into 5 groups: Group 1, del(3p) syndrome; Group 2, BMRS, Ohdo type, limited to the original patients of Ohdo et al. (1986); Group 3, BMRS, Say-Barber-Biesecker-Young-Simpson syndrome (SBBYS) with findings previously described by these five authors above and which is also the most distinctive phenotype; Group 4, BMRS, Maat-Kievit-Brunner type type with coarse, triangular face which is characterized by x-linked inheritance, and thus, occurs only in males, it is also caused by mutations in MED12 gene; and Group 5, BMRS, Verloes type, with severe microcephaly, hypsarrhythmia, adducted thumbs, cleft palate, and abnormal genitalia [5,6].

It has since been discovered that mutations in *KAT6B* underlie syndromic disorders such as Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) and the Maat-Kievit-Brunner type of Ohdo syndrome, as well as the Genitopatellar syndrome. All such disorders present with skeletal and craniofacial anomalies that are detectable through radiologic imaging. KAT6B, located on chromosome 10q22.2, encodes a histone acetyltransferase involved in the epigenetic regulation of gene expression during embryogenesis [7].

KAT6B is involved in epigenetic regulation of gene expression, particularly during embryonic organogenesis. It plays a role in chromatin remodeling through acetylation of histone H3 lysine 9 and 14 (H3K9ac, H3K14ac). These epigenetic marks regulate transcription of genes vital for mesenchymal differentiation, osteoblast lineage commitment, and chondrogenesis, explaining the widespread skeletal malformations. Impaired function of KAT6B disrupts the developmental expression of Runx2, a master regulator of bone formation.

At the molecular level, KAT6B possesses a MYST-type HAT domain, a zinc finger, and multiple PHD-type zinc finger domains, which contribute to its chromatin-binding properties and enzymatic activity. These domains enable it to recognize histone tails and recruit additional regulatory proteins to chromatin regions. Importantly, KAT6B functions as part of a multiprotein complex, interacting with scaffold proteins such as BRPF1 (which recruits it to chromatin) and coactivators like ING5 and MEAF6 [8,9]. Pathogenic variants are often heterozygous mutations that tend to cluster in the C-terminal region, resulting in truncated proteins that lack regulatory domains but retain partial activity.

KAT6B regulates RUNX2, the master transcription factor for osteoblast differentiation [10], thus explaining the multiple skeletal findings. It interacts with CBP/p300, which acetylate histones

during endochondral ossification [11]. Scoliosis or kyphosis may develop in later childhood and should be monitored via serial standing spinal X-rays.

KAT6B is ubiquitously expressed, even in the ventricular zone (neural stem cell niche) of the fetal brain, consistent with the intellectual disability seen in in KAT6B-related disorders. Also, neural crest cell–derived craniofacial structures are especially vulnerable to KAT6B dysregulation, leading to developmental arrest of the first and second branchial arches. Mutations may lead to hypoplastic nasal bones and a flattened nasal bridge, contributing to a depressed midface profile. Micrognathia and retrognathia may also be seen. Delayed dental eruption and oligodontia can be assessed via panoramic radiography. Maxillary hypoplasia contributes to dental malocclusion, visualized as Class III skeletal relationship on cephalometry. Blepharophimosis may result from failed eyelid separation (week 10 – 12), which relies on FOXL2, in turn affected by *KAT6B* mutations [12].

The diagnosis of this disorder is based solely on clinical findings consistent with the SBBYSS group of disorders and genetic testing showing presence of a heterozygous pathogenic variant in *KAT6B* gene. Criteria for clinical diagnosis previously proposed include the mandatory findings of blepharophimosis, ptosis, and intellectual disability and the supporting findings of depressed nasal bridge, hypoplastic teeth, deafness, undescended testes, and hypotonia. Individuals with two major features, or one major feature and two minor features are likely to have a *KAT6B* pathogenic variant [13].

Additional imaging studies including skeletal survey and pelvic ultrasound could be helpful in identifying skeletal and gynecologic manifestations of the syndrome, respectively. Laboratory examinations including thyroid function test could also rule in the presence of hypothyroidism. 2D-echocardiography can also be used to detect presence of cardiac anomalies associated with Ohdo syndrome (ventricular septal defect is the most common cardiac anomaly). Finally, psychometric examinations to assess the level of intellectual disability. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variant in the family.

To date, no definitive treatment has been proposed as this condition is congenital and a genetic mishap. Educational intervention and speech therapy beginning in infancy because of the high risk for motor, cognitive, speech, and language delay should be done. Referral to an orthopedist for consideration of surgical release of contractures, if present, is also suggested. Orchiopexy should be done in males with undescended testes. The patient should also be referred to cardiologists for the management of cardiac problems. Ptosis surgery and cleft palate

repair if present, is also suggested. Other interventions, such as hearing aids as needed for hearing loss, thyroid hormone replacement and genetic counselling, are recommended.

ETHICS COMMITTEE APPROVAL

This report was conducted in accordance with institutional ethical standards of Manila Doctors Hospital, and was approved by tits institutional review board.

INFORMED CONSENT

Written informed consent was obtained from the mother of the patient for publication of this case report and accompanying images.

COMPETING INTERESTS

The authors declare no competing interests.

FUNDING

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DATA AVAILABILITY STATEMENT

All photographs and radiographs pertaining to this study are available in the Harvard Dataverse repository at https://doi.org/10.7910/DVN/ISCGOQ.

AUTHORS CONTRIBUTIONS STATEMENT

Terence Burgo was responsible for Investigation, Resources, Supervision, Writing – Original Draft, and Writing – Review & Editing. Brian Pollo contributed to contributed to Conceptualization, Data Curation, Literature Review, Writing – Original Draft, and Writing – Review & Editing. Both authors approved the final version of the manuscript.

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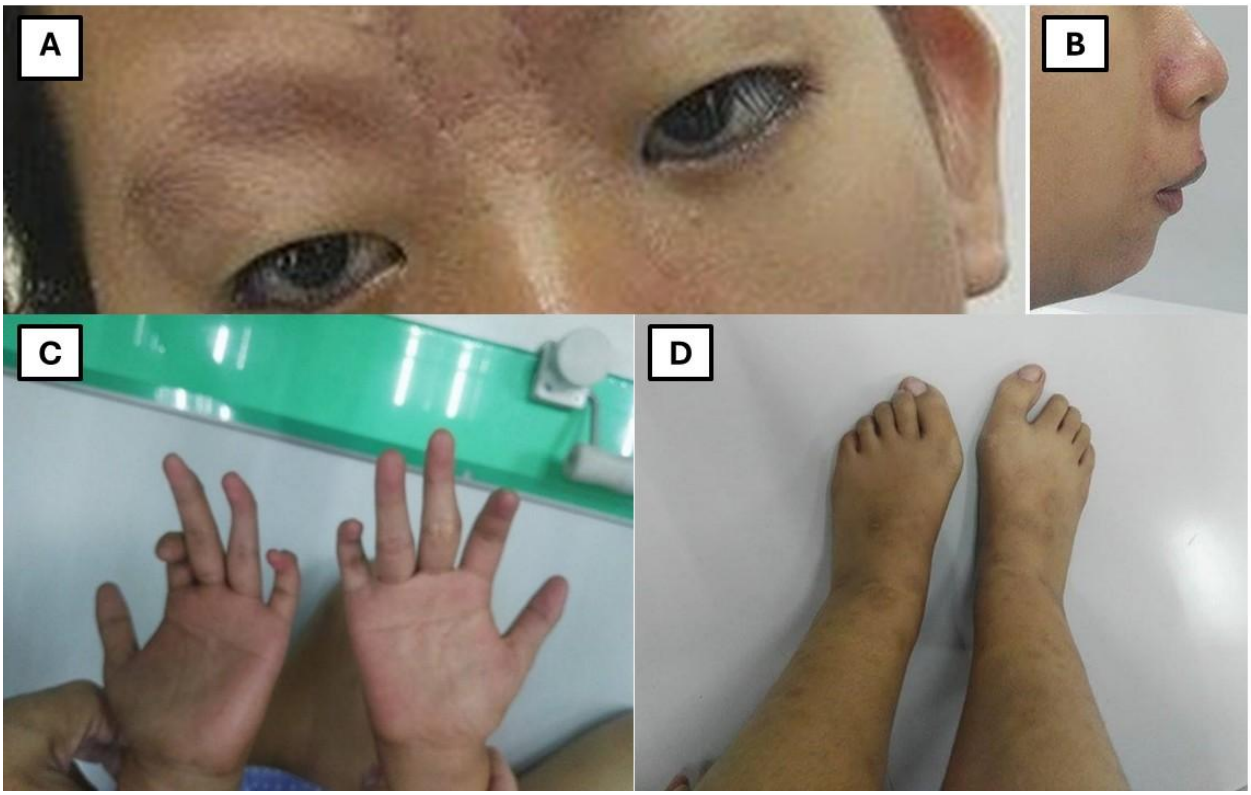

Figure 1. Physical examination findings reveal craniofacial and skeletal abnormalities, including (A) blepharophimosis and ptosis, intermittent nystagmus, broad nasal bridge, (B) rounded nose tip, micrognathia, (C) relatively long thumbs, single palmar crease, atrophic hypothenar and thenar muscles, stiff phalangeal joints, and (D) large first toes.

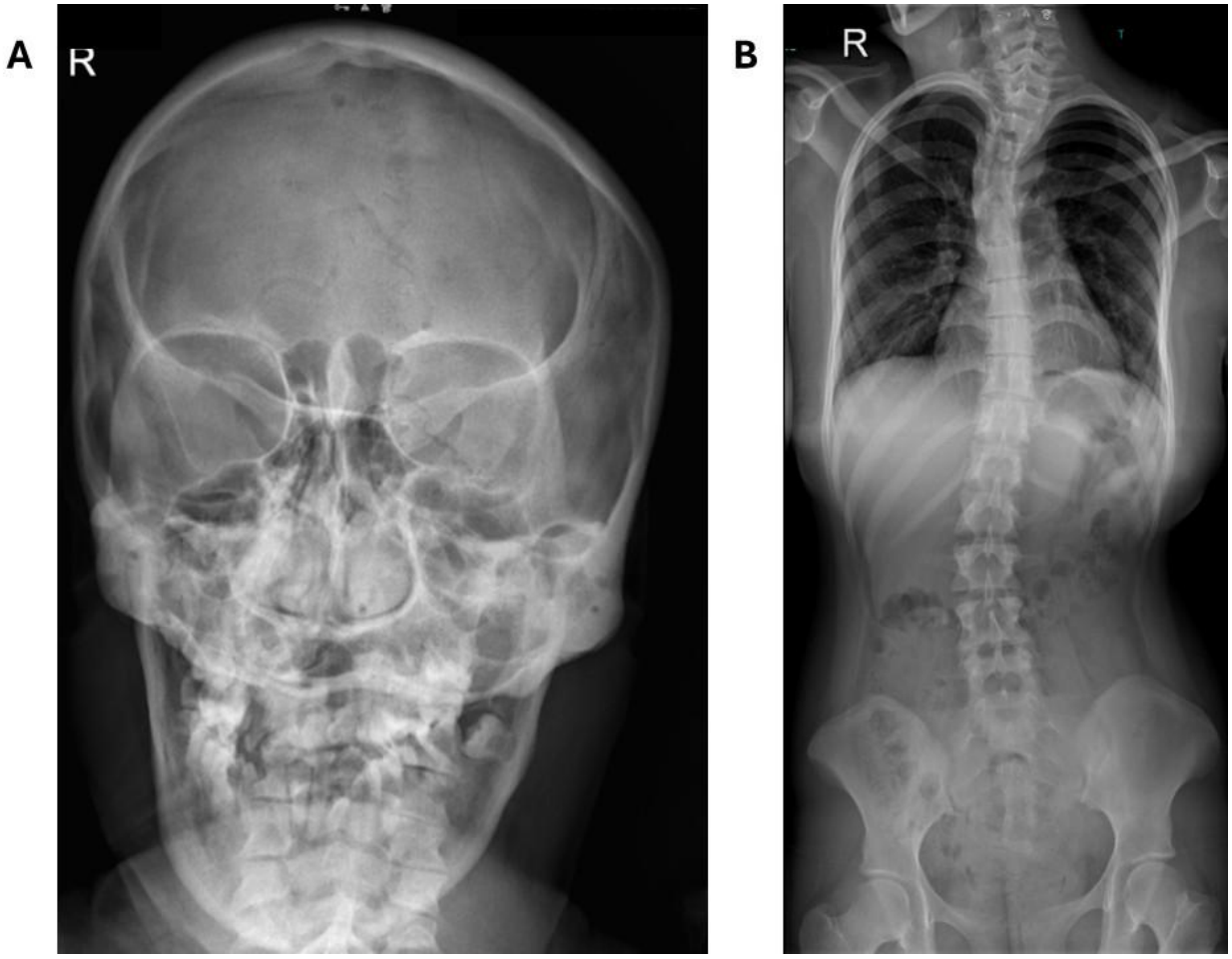

Figure 2. Composite survey results of the axial skeleton. Radiographs of the skull AP (A), and thoracolumbar spine AP (B) reveal abnormalities. Notable findings include micrognathia (A) and scoliosis (B).

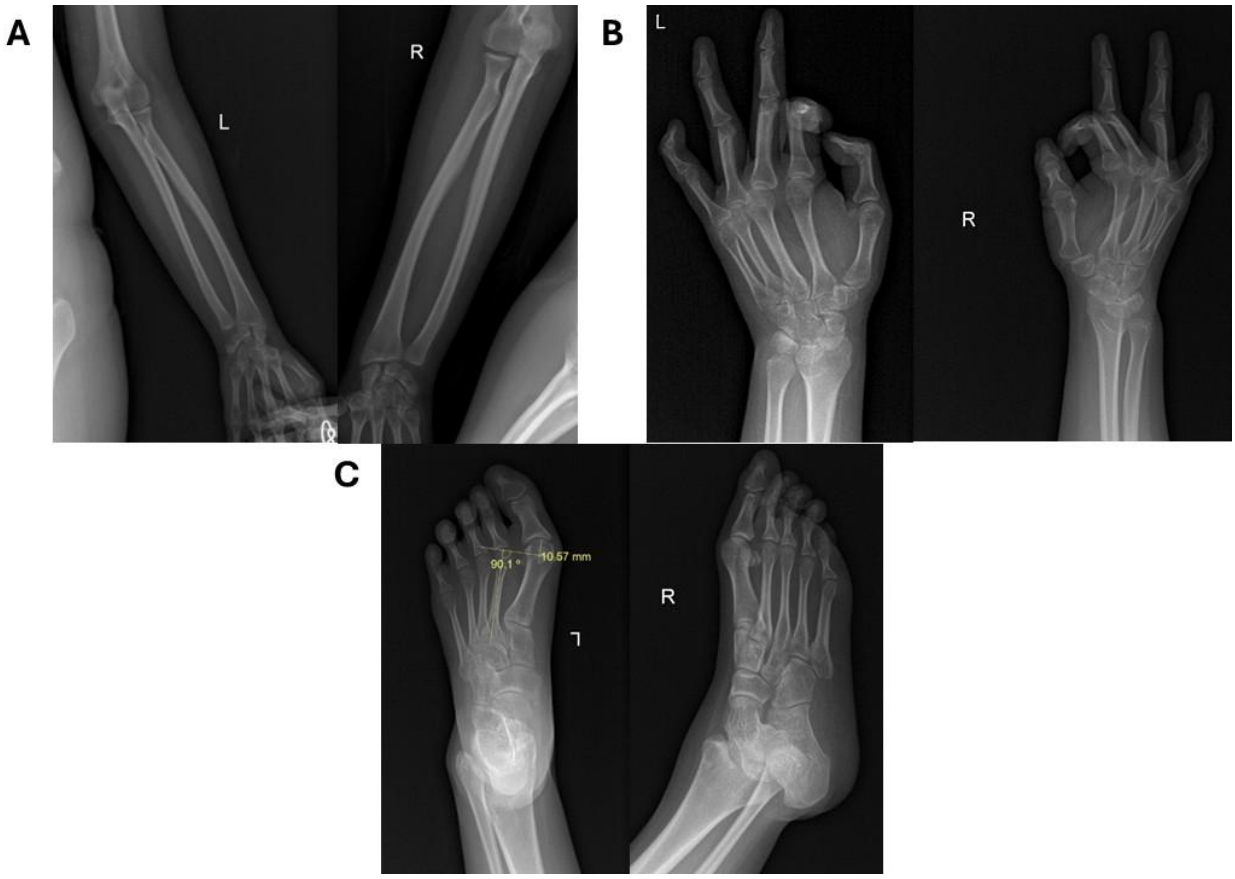

Figure 3. Composite skeletal survey results of the appendicular skeleton. Radiographs of the radius-ulna AP (A), hands AP (B), and feet APL (C) reveal further generalized abnormalities. Notable findings include negative ulnar variance (A) and bilateral hallux valgi deformity (C). The distal phalanges of both 2nd digits of the hands are shortened (B).

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