Rwanda Medical Journal RMJ

CASE REPORT Open Access

A Novel Pathogenic Variant in EXT1 Causing Autosomal Dominant Multiple Hereditary Exostoses in a 5-Year-Old Rwandan Patient

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ABSTRACT

INTRODUCTION: Hereditary multiple osteochondromas (HMO) is a rare autosomal dominant skeletal disorder characterized by the development of multiple cartilage-capped bony outgrowths caused predominantly by pathogenic variants in the EXT1 or EXT2 genes. Although molecular diagnosis has become increasingly accessible worldwide, genetically confirmed cases from sub-Saharan Africa remain scarce, limiting knowledge of the regional mutational spectrum.

CASE PRESENTATION: We report the case of a 5-year-old Rwandan girl who presented with progressively enlarging, painless bony swellings involving both knees and the right clavicle, accompanied by bilateral genu valgum. Radiographs demonstrated multiple osteochondromas affecting the distal femora, proximal tibiae, fibulae, and ulna, consistent with hereditary multiple osteochondromas. Conventional cytogenetic analysis showed a normal female karyotype (46,XX). Targeted next-generation sequencing identified a novel heterozygous frameshift variant in EXT1(NM_000127.2:c.640del; p.Ala214ArgfsTer38). The variant was absent from population databases and was classified as likely pathogenic according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) criteria (PVS1 and PM2), confirming the diagnosis of autosomal dominant hereditary multiple osteochondromas type 1 (OMIM #133700). The patient was managed through a multidisciplinary team with orthopedic follow-up and genetic counseling.

CONCLUSION: This report presents the first molecularly confirmed case of hereditary multiple osteochondromas in Rwanda, identifying a novel likely pathogenic EXT1 variant. It demonstrates the value of genomic testing for accurate diagnosis, multidisciplinary management, genetic counseling, and long-term surveillance, while expanding the representation of African populations in global genomic variant databases.

Keywords: Hereditary multiple osteochondromas, hereditary multiple exostoses, EXT1, next-generation sequencing, skeletal dysplasia, genomics, Rwanda, case report

***Equal contribution; &Corresponding author:** Prof. Leon Mutesa, MD, PhD, FAAS. Center for Human Genetics and Genomics, School of Medicine and Pharmacy, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: no funding was sought; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable; **Originality:** All authors: this manuscript is original has not been published elsewhere; **Review:** This manuscript was peer-reviewed by three reviewers in a double-blind review process.

Received: 9th June2026; **Initial decision given:** 17th June 2026; **Revised manuscript received:** 24th June 2026; **Accepted:** 29th June 2026.

 Publisher: Africa Health Sciences University (AHSU), Kigali Rwanda. ISSN: 2079-097X (print); 2410-8626 (online)

Citation for this article: Pierre Roger Kayumba; Hannah Umutoni Mugaragu; Cheryl Shenge Valois et al. A Novel Pathogenic Variant in EXT1 Causing Autosomal Dominant Multiple Hereditary Exostoses in a 5-Year-Old Rwandan Patient. Rwanda Medical Journal, Vol. 83, no. 2, p. 5-11, 2026. https://dx.doi.org/10.4314/rmj.v83i2.1

INTRODUCTION

Osteochondromas are the most common benign bone tumors, accounting for approximately 20–50% of all benign bone neoplasms and nearly 10% of primary bone tumors worldwide [1]. Although traditionally classified as tumors, osteochondromas are now recognized as developmental abnormalities arising from aberrant cartilage growth at the growth plate due to defective endochondral ossification [2]. They typically present as cartilage-capped bony projections that maintain cortical and medullary continuity with the parent bone and usually develop during childhood and adolescence before ceasing growth after skeletal maturity [3].

Osteochondromas occur either as solitary lesions or as part of hereditary multiple osteochondromas (HMO), also known as hereditary multiple exostoses (HME), a rare autosomal dominant skeletal disorder with an estimated prevalence of approximately 1 in 50,000 individuals [3,4]. HMO is predominantly caused by pathogenic variants in the EXT1 and EXT2 genes, which encode glycosyltransferases essential for heparan sulfate biosynthesis. Loss of function of these genes disrupts normal chondrocyte proliferation, differentiation, and growth plate organization, resulting in the formation of multiple osteochondromas around the metaphyses of long bones [5,6].

Clinically, HMO is characterized by multiple painless bony prominences, limb-length discrepancy, angular deformities, restricted joint mobility, and short stature, with symptoms often becoming evident during the first decade of life [3,4]. While many lesions remain asymptomatic, larger osteochondromas may cause pain, mechanical irritation, neurovascular compression, tendon impingement, or skeletal deformities requiring surgical intervention [1]. Furthermore, patients with HMO carry a lifetime risk of approximately 2–5% of malignant transformation to secondary peripheral chondrosarcoma, emphasizing the importance of early diagnosis and long-term surveillance [7].

Advances in molecular diagnostics, particularly next-generation sequencing (NGS), have improved the identification of pathogenic EXT1 and EXT2 variants, enabling accurate diagnosis, genetic counseling, and individualized clinical management [8,9]. However, genomic characterization of HMO remains scarce in sub-Saharan Africa, where access to clinical genetics services and molecular testing is still limited. Consequently, the spectrum of pathogenic variants among African populations remains poorly understood, and many patients experience prolonged diagnostic delays. This knowledge gap underscores the need to document genetically confirmed cases from underrepresented populations.

Here, we report the first molecularly confirmed case of hereditary multiple osteochondromas in Rwanda caused by a novel heterozygous frameshift variant in EXT1 (NM_000127.2:c.640del; p.Ala214ArgfsTer38). This case highlights the clinical utility of genomic testing in children with skeletal dysplasia, expands the mutational spectrum of EXT1, and contributes valuable evidence toward improving the diagnosis and management of rare genetic skeletal disorders in sub-Saharan Africa.

CASE PRESENTATION

A five-year-old Rwandan girl was referred to the Clinical Genetics Unit at Rwanda Military Teaching Hospital for evaluation of progressively enlarging bony masses involving both lower limbs. The lesions were painless and had not affected her ability to walk or perform age-appropriate daily activities. The referral was made to establish the underlying diagnosis and guide further management.

The patient was the first child of healthy, non-consanguineous parents. She was born at term through spontaneous vaginal delivery with a birth weight of 3.2 kg. The pregnancy, delivery, and neonatal period were uneventful, with no history of birth asphyxia, neonatal intensive care admission, or developmental delay. Her developmental milestones were achieved appropriately for age. There was no known family history of hereditary skeletal disorders, congenital anomalies, recurrent fractures, short stature, or similar bony swellings among first- or second-degree relatives.

According to her mother, multiple bony prominences around both knees were first noticed approximately one year before presentation, when the patient was four years old. The swellings gradually increased in size over time but remained painless. There was no history of preceding trauma, fever, weight loss, constitutional symptoms, or limitation of physical activity. Shortly before presentation, the parents reported intermittent episodes of perineal numbness, raising concern

for possible neural compression by an underlying pelvic or spinal lesion, although no associated bowel or bladder dysfunction was reported.

On physical examination, the patient appeared well, with normal nutritional status and stable vital signs. She demonstrated a normal gait despite bilateral genu valgum. Multiple hard, non-tender, immobile bony prominences were palpable around the distal femora and proximal tibiae bilaterally, as well as over the right clavicle. The overlying skin

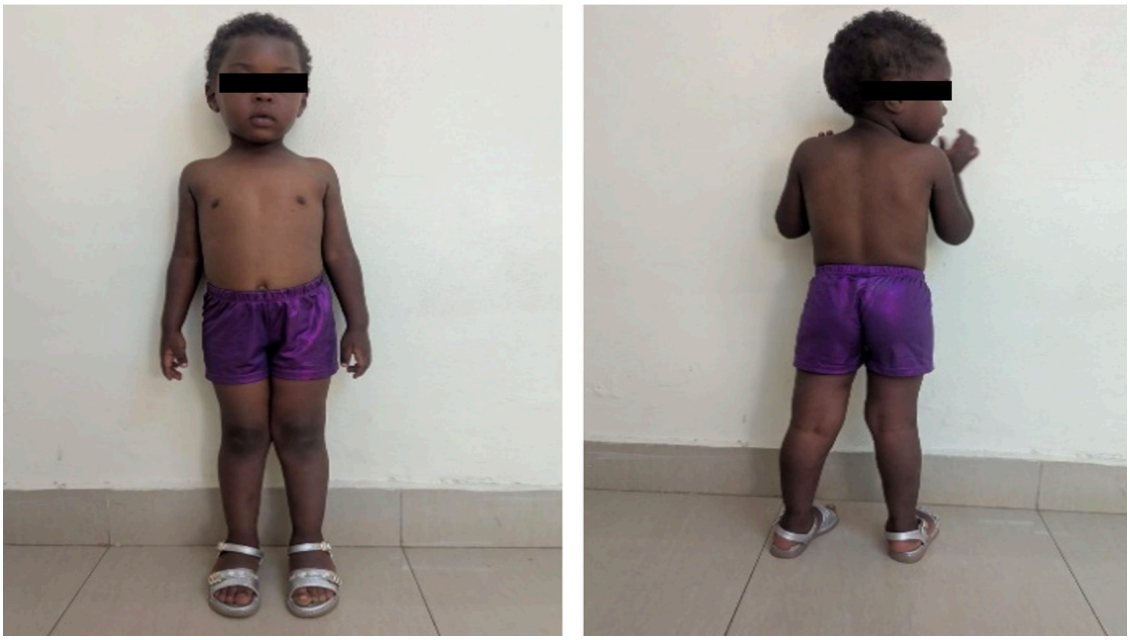

Figure 1: Clinical photographs showing bilateral bony prominences (exostoses) around the knee joints in the proband.

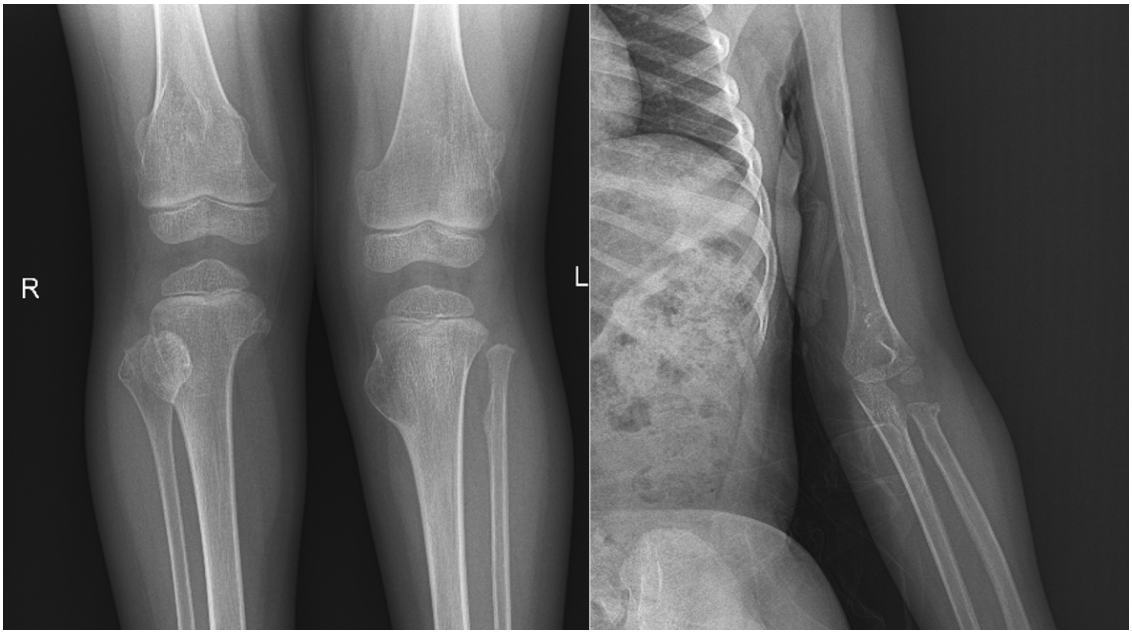

Figure 2: Skeletal x-rays images (a) showing bilateral bony prominences (exostoses) on the proximal part of tibia, fibula and distal femur (b) showing unilateral bony prominence (exostoses) on the proximal part of ulna in the proband.

was intact without erythema or tenderness. Both knee joints had full active and passive ranges of motion without pain or instability. No neurological deficits were detected on routine examination, and distal neurovascular status of both lower limbs was preserved. The remainder of the systemic examination was unremarkable. Clinical photographs illustrating the skeletal deformities are presented in Figure 1.

Plain radiographs of the affected limbs demonstrated multiple sessile and pedunculated osteochondromas involving the distal femora bilaterally, the proximal tibiae, proximal fibulae, and the proximal ulna, with preserved cortical and medullary continuity between the lesions and the parent bones, findings highly suggestive of hereditary multiple osteochondromas (Figure 2). No radiographic features suspicious for malignant transformation, such as cortical destruction, irregular mineralization, or soft tissue masses, were observed.

Given the presence of multiple osteochondromas at a young age, hereditary multiple osteochondromas was strongly suspected. Differential diagnoses considered included metachondromatosis, Langer–Giedion syndrome (trichorhinophalangeal syndrome type II), fibrodysplasia ossificans progressiva, and other hereditary skeletal dysplasias associated with multiple exostoses. The absence of characteristic craniofacial abnormalities, soft tissue ossification, or syndromic manifestations made these alternative diagnoses less likely.

After genetic counseling, peripheral blood samples were collected for conventional karyotyping and molecular genetic analysis. Cytogenetic evaluation demonstrated a normal female karyotype (46,XX). Targeted next-generation sequencing using the CentoDysmorph clinical exome panel identified a heterozygous frameshift variant in EXT1 (NM_000127.2:c.640del; p.Ala214ArgfsTer38) (Table 1). The variant was absent from population databases and was classified as likely pathogenic according to ACMG/AMP criteria (PVS1 and PM2), confirming the diagnosis of autosomal dominant hereditary multiple osteochondromas type 1 (OMIM #133700).

The patient was subsequently referred for multidisciplinary management involving clinical genetics, pediatric orthopedics, physiotherapy, and rehabilitation services. The family received post-test genetic counseling regarding the autosomal dominant inheritance pattern, recurrence risk, and the importance of long-term clinical follow-up to monitor skeletal growth, functional impairment, and potential malignant transformation. At the most recent follow-up, the patient remained ambulatory without functional limitations, and conservative management with regular orthopedic surveillance was recommended pending future clinical progression.

Written informed consent was obtained from both parents, and age-appropriate assent was obtained from the patient before blood sample collection. All data and images were de-identified to protect patient confidentiality. The study was conducted in accordance with the principles of the Declaration of Helsinki.

DISCUSSION

Approximately 90% of genetically confirmed cases of HMO are caused by pathogenic variants in EXT1 or EXT2, with EXT1 variants generally associated with a more severe clinical phenotype, including a higher number of exostoses, greater skeletal deformity, shorter stature, and an increased likelihood of requiring surgical intervention [10,11]. The present report describes the first molecularly confirmed case of HMO in Rwanda and identifies a previously unreported heterozygous frameshift variant, EXT1 c.640del (p.Ala214ArgfsTer38). This deletion introduces a premature termination codon early in the coding sequence, resulting in

Table 1: Sequence variant identified in the proband

Gene	Variant Coordinates	Amino Acid Change	SNP Identifier	Zygosity	In Silico Parameters	Allele Frequencies	Type and Classification
EXT1	NM_000127.2: c.640del	p.(Ala214ArgfsTer38)	N/A	Heterozygous	PolyPhen: N/A SIFT: N/A MutationTaster: N/A	gnomAD: absent ESP: absent 1000G: absent	Frameshift Likely pathogenic

truncation of the EXT1 protein. Because loss-of-function is a well-established disease mechanism for EXT1-associated HMO, this variant fulfills the ACMG/AMP criteria for likely pathogenicity, particularly PVS1 (null variant in a gene where loss of function is a known mechanism of disease) and PM2 (absence from population databases) [12]. The absence of this variant from gnomAD [13], 1000 Genomes [14], and other publicly available databases further supports its novelty and expands the mutational spectrum of EXT1.

EXT1 encodes exostosin-1, a glycosyltransferase that functions together with EXT2 in the polymerization of heparan sulfate chains. Heparan sulfate proteoglycans regulate multiple developmental signaling pathways, including Indian Hedgehog (IHH), fibroblast growth factor (FGF), bone morphogenetic protein (BMP), Wnt, and parathyroid hormone-related protein (PTHrP), all of which are essential for normal growth plate organization and endochondral ossification [5,6]. Loss of EXT1 function disrupts these signaling pathways, resulting in abnormal chondrocyte proliferation and ectopic cartilage formation that subsequently develops into osteochondromas. This molecular mechanism explains the early childhood onset and progressive accumulation of lesions observed in our patient.

Clinically, our patient presented at five years of age with multiple painless exostoses affecting the distal femora, proximal tibiae, fibulae, ulna, and clavicle, accompanied by bilateral genu valgum. These findings are consistent with the classical phenotype of HMO, in which lesions most commonly occur around the knee, accounting for nearly half of all osteochondromas [1,4]. Although clavicular involvement is uncommon compared with long bones, it has been reported in patients with extensive disease and supports the diagnosis of hereditary rather than solitary osteochondroma [2]. The intermittent perineal numbness described by the family also highlights the possibility of neurovascular compression, one of the recognized complications of HMO that warrants careful clinical and radiological surveillance [15].

An important aspect of this case is the absence of a known family history despite the autosomal dominant inheritance pattern of HMO. Approximately 10–20% of patients harbor de novo pathogenic variants, while incomplete family history may also reflect reduced penetrance, variable expressivity, or previously undiagnosed mildly affected relatives [11,16]. Ideally, cascade genetic testing of both parents would distinguish between inherited and de novo disease; however, parental molecular testing was not available in our setting.

Radiographic evaluation remains the cornerstone of diagnosis because osteochondromas demonstrate characteristic cortical and medullary continuity with the parent bone. Nevertheless, molecular confirmation has become increasingly important, particularly in children with atypical clinical features or in populations where skeletal dysplasias are underrecognized. Identification of the causal pathogenic variant establishes a definitive diagnosis, facilitates genetic counseling, informs recurrence risk assessment, and enables appropriate long-term surveillance for complications [17].

Although osteochondromas are benign lesions, patients with HMO remain at increased risk of skeletal deformities, limb-length discrepancy, restricted joint mobility, fractures, bursitis, vascular compromise, and neurological complications [10]. Of greatest clinical concern is malignant transformation to secondary peripheral chondrosarcoma, which occurs in approximately 2–5% of patients with hereditary disease compared with less than 1% of solitary osteochondromas [7]. Warning signs include persistent pain, rapid lesion enlargement after skeletal maturity, increasing cartilage cap thickness (>2 cm in adults), cortical destruction, and adjacent soft tissue masses. Recognition of these features should prompt advanced imaging and surgical evaluation.

This case also highlights the growing role of genomic medicine in resource-limited settings. Access to next-generation sequencing remains limited across much of sub-Saharan Africa, resulting in prolonged diagnostic odysseys for patients with rare genetic disorders. The successful molecular diagnosis achieved in this patient demonstrates the feasibility and clinical value of integrating genomic testing into tertiary healthcare systems in Rwanda. Beyond improving patient care, reporting novel African variants contributes to reducing the underrepresentation of African populations in global genomic databases, thereby improving variant interpretation for future patients.

Only a few genetically documented HMO cases have been reported from sub-Saharan Africa, including isolated reports from Nigeria and Senegal [18,19]. Consequently, the molecular epidemiology

of EXT1 and EXT2 variants in African populations remains poorly characterized. Our report therefore represents an important contribution to the regional literature by documenting a novel pathogenic EXT1 variant from Rwanda and further emphasizing the need for multicenter genomic studies investigating skeletal dysplasias across Africa.

CONCLUSION

This case underscores the importance of considering HMO in children presenting with multiple painless bony swellings and skeletal deformities. Early referral for clinical genetics assessment and molecular testing can substantially shorten the diagnostic journey, facilitate multidisciplinary management, enable family counseling, and improve surveillance for long-term complications. As genomic medicine continues to expand across Africa, documenting novel pathogenic variants such as EXT1 c.640del (p.Ala214ArgfsTer38) will enhance understanding of disease diversity and strengthen global variant databases.

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