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Knuckle, Knuckle, Dimple, Dimple: Do Not Miss A Diagnostic Opportunity

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ABSTRACT

Turner syndrome (TS) often presents with subtle or overlooked clinical signs, contributing to frequent diagnostic delays. We describe the case of a 13-year-old girl referred for short stature whose only remarkable physical findings were the absence of the fourth and fifth knuckles on both hands—known as Archibald's metacarpal sign—and a short fourth metatarsal. Growth had decelerated after spontaneous menarche, and previous examinations had not recognized these skeletal clues. Radiographs confirmed short fourth and fifth metacarpals. Karyotype analysis identified a complete deletion of the short arm of one X chromosome (Xp), consistent with TS. Further evaluation revealed a bicuspid aortic valve, autoimmune thyroiditis with subclinical hypothyroidism, and reduced ovarian reserve. Archibald's sign, caused by SHOX haploinsufficiency, is present in about one-third of individuals with TS but may also appear in other disorders or even healthy individuals. This case highlights the diagnostic value of careful physical examination in girls with short stature. Recognizing seemingly minor skeletal findings can prompt timely karyotyping, allowing earlier detection of TS and appropriate long-term management.

1 | Introduction

Genetic causes account for a substantial proportion of pediatric short stature; recent studies indicate that approximately one quarter to two fifths of children previously labeled as having idiopathic short stature receive a molecular diagnosis after comprehensive evaluation [1, 2]. Identifying the underlying genetic defect is therefore crucial for accurate diagnosis, individualized management, and appropriate family counseling, although the diagnostic pathway is often complex and stepwise, combining clinical assessment, hormonal work-up, and targeted or broad genetic testing [3, 4].

Short stature may also occur as part of syndromic presentations [3, 4]. A paradigmatic example is Turner syndrome (TS), a chromosomal condition due to complete or partial monosomy X and one of the most common genetic causes of short stature in females [5, 6]. Despite well-described clinical features, diagnosis is frequently delayed, especially in girls with mild or incomplete phenotypes who lack the classic stigmata [5, 7]. The "classical" presentation—short stature, gonadal dysgenesis, characteristic facies, and left-sided cardiac defects—likely represents only a minority of cases, whereas most girls show variable or subtle manifestations [5]. For this reason, chromosome analysis should be considered in any girl with unexplained growth failure, irrespective of the presence of obvious dysmorphic features [2, 5].

Among these subtle signs, skeletal anomalies linked to haploinsufficiency of the SHOX gene, located in the pseudoautosomal region of Xp, are particularly informative but may be easily overlooked during routine visits [3, 4, 8, 9]. One of the most characteristic findings is Archibald's metacarpal sign (AMS)—the classic "knuckle, knuckle, dimple, dimple" appearance—caused by relative shortening of the fourth and fifth metacarpals [10–14]. AMS may serve as an early physical clue to TS. Radiographic studies by Poznanski and colleagues detailed the pattern of

Key Clinical Message

In girls with unexplained short stature, Archibald's metacarpal sign ("knuckle, knuckle, dimple, dimple") may be the only visible clue to Turner syndrome, even with spontaneous puberty and regular menses. Careful hand examination and timely karyotyping enable earlier diagnosis, comorbidity screening, and fertility counseling.

metacarpal shortening in endocrine and genetic disorders, showing that specific combinations of shortened metacarpals can help differentiate TS from other conditions such as pseudohypoparathyroidism, brachydactyly E, and acrodysostosis [15]. Additional skeletal signs, such as a short fourth metatarsal or Madelung deformity, may further increase suspicion [16].

A meticulous physical examination remains essential to detect these minor skeletal findings and to guide targeted diagnostic testing [3, 4]. This report describes a 13-year-old girl referred for short stature in whom AMS and a short fourth metatarsal were the only remarkable physical findings, ultimately leading to the diagnosis of TS.

2 | Case History and Examination

A 13-year-old girl was referred for evaluation of short stature (height −2.06 SDS). She was born at term with appropriate weight and length. Linear growth tracked along the 10th percentile from early childhood up to 11 years of age, when a clear deceleration became evident after spontaneous menarche. Target height, based on parental stature, was 0.41 SDS, and there was no family history of short stature, delayed puberty, or skeletal anomalies.

She was asymptomatic, with a normal body mass index. Blood pressure and systemic examination were within normal limits. Tanner stage was B4, with regular, monthly menstrual cycles and no history of primary amenorrhea, suggesting apparently normal pubertal progression. Apart from auxological data, physical examination was unremarkable except for the dorsum of both hands, which exhibited a typical "knuckle, knuckle, dimple, dimple" aspect when she made a fist (Figure 1), and a short fourth metatarsal of the left foot. These skeletal signs had not been previously recognized or considered clinically relevant in earlier evaluations.

3 | Differential Diagnosis, Investigations, and Treatment

In an adolescent girl with short stature, spontaneous puberty, and an otherwise unremarkable examination aside from subtle skeletal anomalies, the initial differential diagnosis included familial short stature, isolated SHOX haploinsufficiency (including Léri–Weill dyschondrosteosis), and early or mild forms of syndromic short stature, particularly TS, including mosaic variants [3, 5]. Other genetic or metabolic conditions classically associated with AMS—such as Albright hereditary osteodystrophy and pseudopseudohypoparathyroidism, acrodysostosis, brachydactyly E, homocystinuria, and thalassemia major—as well as post-infective, post-infarction, and post-traumatic causes were also considered, as summarized in Table 1 [10–15].

Radiographs of the hands and feet were obtained to further characterize the skeletal anomalies. Imaging confirmed shortening of the fourth and fifth metacarpals and a short fourth metatarsal, consistent with the presence of AMS. Radiological anthropometry, as previously described in TS cohorts, showed a pattern of relative shortening of the lateral metacarpals compatible with SHOX-related bone changes [11, 13, 15]. Although AMS can be seen in several congenital and acquired disorders and in up to approximately 5%–10% of otherwise healthy individuals [10, 11, 14], its presence in a girl with unexplained short stature substantially increased the clinical suspicion of TS [5, 14].

Conventional karyotype analysis was therefore performed and demonstrated a complete deletion of the short arm of one X chromosome (Xp), confirming the diagnosis of TS within the spectrum of Xp-deletion karyotypes [8, 9]. Subsequent targeted investigations identified additional TS-related comorbidities. Echocardiography revealed a bicuspid aortic valve with mild

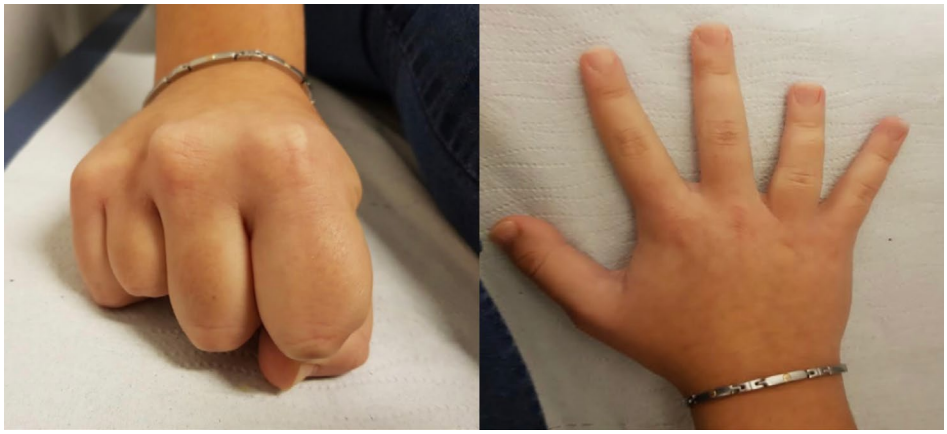

FIGURE 1 | Archibald's metacarpal sign in our patient. It consists of dimpling over the clenched fist's knuckles and it is due to the shortening of the fourth and fifth metacarpals than the third one.

TABLE 1 | Conditions associated with the presence of Archibald's metacarpal sign.

Endocrine conditions	– Turner Syndrome – Pseudohypoparathyroidism (Albright's hereditary osteodystrophy) and pseudopseudohypoparathyroidism – Male hypogonadism/undescended testis
Congenital conditions	– Basal cell nevus syndrome (Gorlin syndrome) – Acrodysostosis – Brachydactyly – Trichorhinophalangeal type 2 (Langer-Giedion syndrome) – Hereditary multiple exostosis syndrome – Homocystinuria
Acquired Disorders (*acute or chronic conditions, particularly those involving growth plate*)	– Post-infective (osteomyelitis, yaws, tuberculosis dactylitis) – Post-infarction (sickle cell disease) – Post-traumatic – Juvenile idiopathic arthritis
Normal variant	– Idiopathic

aortic stenosis, a finding consistent with the known association between Xp deletions and left-sided obstructive lesions [17–19]. Laboratory evaluation showed autoimmune thyroiditis with subclinical hypothyroidism, in line with the increased prevalence of autoimmune thyroid disease in TS [20, 21]. Reproductive hormone assessment and anti-Müllerian hormone levels indicated reduced ovarian reserve, supporting the high risk of premature ovarian insufficiency in girls and young women with TS, even those with partial monosomy [8, 9, 22].

Given the advanced bone age and limited residual growth potential, growth hormone therapy was not initiated, consistent with guideline recommendations that emphasize timing of treatment to maximize height gain [5, 23]. Management focused on comprehensive evaluation and surveillance of associated conditions. Cardiology follow-up was arranged to monitor valve function and aortic dimensions. Endocrine follow-up was planned to monitor growth, thyroid status, and pubertal evolution. The patient was referred to a fertility clinic to discuss reproductive prognosis and early fertility-preservation options in view of the diminished ovarian reserve [5, 22].

4 | Outcome and Follow-Up

Following the diagnosis of TS, the patient was enrolled in a structured follow-up program based on current international TS care recommendations [5, 6]. She attends regular endocrine visits for monitoring of growth parameters, thyroid function, pubertal development, and metabolic profile. Thyroid function tests are periodically reassessed to determine if and when levothyroxine replacement will be required, in accordance with recommendations for managing autoimmune thyroid disease in TS [20, 21].

Cardiology follow-up with serial echocardiography was initiated because of the bicuspid aortic valve with mild aortic stenosis, with particular attention to potential progression of valve disease and development of aortic root dilation, both recognized complications in TS and especially in Xp-related karyotypes [17–19]. Reproductive counseling at a dedicated fertility clinic addressed expectations regarding future fertility and discussed options such as oocyte or ovarian tissue cryopreservation to be considered in a timely manner given her already reduced ovarian reserve [5, 22].

Psychological support was offered to the patient and her family to facilitate understanding of the diagnosis, its long-term implications, and the need for ongoing multidisciplinary follow-up. At the latest follow-up, the patient remained clinically stable, with no progression of cardiac or thyroid disease, and was engaged in shared decision-making regarding future fertility-preservation strategies.

5 | Discussion

TS is a chromosomal disorder due to complete or partial monosomy X and is a leading genetic cause of short stature in girls [5, 6]. Despite characteristic clinical features, diagnosis is often delayed, with median ages around early adolescence, particularly in individuals with milder or incomplete phenotypes [5, 7]. The clinical expression of TS is heterogeneous and may include short stature, skeletal anomalies (short fourth or fifth metacarpals and metatarsals, Madelung deformity, scoliosis), craniofacial features, cardiovascular defects, renal anomalies, and autoimmune diseases [5–7, 24].

AMS is a well-recognized skeletal sign in TS and other disorders [10–14]. Clinically, it appears as the apparent absence of the fourth and fifth knuckles on the dorsum of a clenched fist. Radiographically, AMS is confirmed when a tangential line drawn across the heads of the fourth and fifth metacarpals intersects the head of the third metacarpal [10, 15]. Because the lateral metacarpals grow more slowly than the third, the degree of shortening and the prominence of the sign increase with age [13]. AMS is reported in roughly one third of individuals with TS, with similar prevalence in complete and partial monosomy X, whereas it is present in a smaller proportion of otherwise healthy individuals [11, 13, 14]. The presence of AMS should therefore be interpreted within the broader clinical context [14].

The underlying mechanism of many skeletal anomalies in TS is haploinsufficiency of the *SHOX* gene [6, 8, 9]. In the present case, the Xp deletion is consistent with SHOX haploinsufficiency and explains the combination of short stature, metacarpal and metatarsal shortening. However, AMS is not specific for TS and can be observed in a range of endocrine, congenital, acquired, and idiopathic contexts, including pseudohypoparathyroidism, acrodysostosis, brachydactyly E, post-infective or post-infarction bone damage, and juvenile idiopathic arthritis [10, 14–16]. This underscores the need for a structured diagnostic approach, integrating auxology, family history, and targeted investigations rather than relying on a single sign [2, 3].

When a girl presents with unexplained short stature and the presence of AMS, karyotype analysis should be considered a first-line investigation, even in the presence of apparently normal pubertal progression and spontaneous menarche [2, 5]. Mosaicism or partial monosomy can preserve some ovarian function, allowing spontaneous puberty and even pregnancies, and should not preclude cytogenetic evaluation [8, 9]. Genes critical for ovarian maintenance are primarily located on Xq; therefore, Xp deletions, as in this patient, may spare some aspects of ovarian development yet still confer a high risk of premature ovarian insufficiency, as suggested by the reduced ovarian reserve and supported by longitudinal studies of ovarian function in TS [8, 9, 22].

Once TS is diagnosed, a systematic search for associated visceral anomalies is mandatory [5, 6]. Cardiovascular disease, particularly bicuspid aortic valve and aortopathy, represents a major cause of morbidity and mortality and is notably associated with Xp abnormalities and certain karyotypes [17–19]. Autoimmune thyroiditis is common in TS, with reported prevalences of thyroid autoantibodies and hypothyroidism ranging from 15% to 40% and may be more frequent in individuals with specific karyotypic patterns [20, 21, 25]. The comorbidities identified in this patient—bicuspid aortic valve, autoimmune thyroiditis, and reduced ovarian reserve—align with these known genotype–phenotype correlations in Xp-deletion TS [8, 17, 18, 20].

This case illustrates how subtle skeletal signs, such as AMS, can be the only visible clue to an underlying chromosomal disorder. Failure to examine the hands and feet carefully may delay recognition of TS, postponing essential screening for cardiovascular and endocrine complications and missing the window for fertility-preservation counseling [4, 5]. By contrast, early recognition of AMS in the context of short stature can trigger timely karyotyping, comprehensive evaluation, and anticipatory guidance. Integrating systematic hand and foot inspection into the routine assessment of children with growth failure is a low-cost, high-yield strategy that can change the diagnostic trajectory.

6 | Conclusion

The presence of AMS in a girl with unexplained short stature should immediately raise suspicion of TS and prompt karyotype testing, even when puberty and menses are spontaneous and apparently normal. Early diagnosis not only reveals otherwise unrecognized comorbidities, such as cardiovascular anomalies and autoimmune thyroiditis, but also creates opportunities to optimize final height when timing allows, to monitor cardiovascular and endocrine risks, and to discuss fertility-preservation options at an appropriate time. Careful inspection of the hands and feet should therefore be considered a routine component of the physical examination in any child or adolescent presenting with short stature.

Author Contributions

Maria Chiara Pellegrin: conceptualization, writing – original draft. **Gianluca Tamaro:** data curation, investigation, writing – original draft. **Alice Fachin:** data curation, investigation, writing – original draft. **Egidio Barbi:** supervision, writing – review and editing. **Gianluca Tornese:** data curation, supervision, supervision, validation, validation, writing – review and editing, writing – review and editing.

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Ethics Statement

As a single-case report with the patient's signed consent, no other ethical review was required.

Consent

Written informed consent was obtained from the patient's parents for the publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data used in this article are available upon request from the authors.

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