

Clinical profile of McCune-Albright syndrome in Chinese pediatric patients: A single-center retrospective study

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Abstract

Background

McCune-Albright syndrome (MAS) is a rare mosaic disorder caused by somatic gain-of-function mutations in *GNAS*, characterized by café-au-lait macules, fibrous dysplasia (FD), and peripheral precocious puberty (PP). Data on Chinese pediatric MAS patients remain limited.

Methods

This retrospective study described clinical profile, treatment, and genetic findings in 66 pediatric MAS patients at our center.

Results

The cohort included 56 females and 10 males, with median age of 5.18 years. PP and café-au-lait macules were the most common manifestations (84.8%), followed by FD (53.0%), thyroid lesions (12.1%), neonatal hypercortisolism (3.0%), and GH excess (1.5%). PP predominated in females (96.4% vs. 20.0%, $p < 0.001$), whereas FD was more common in males (90.0% vs. 46.4%, $p = 0.015$). The classic triad occurred in 21.2% of patients, whereas dyad presentations accounted for 65.1%. Nine of 56 patients with peripheral PP developed central PP. Two male infants with neonatal hypercortisolism required adrenalectomy. *GNAS* mutations were detected in 5.6% of peripheral blood samples but in all 3 bone tissue samples tested.

Conclusions

As the largest single-center Chinese pediatric MAS cohort, these findings paralleled Western reports with striking sex-specific prevalence differences. Incomplete presentations warrant diagnostic vigilance, tissue-based genetic testing should be prioritized, and long-term endocrine surveillance is essential.

Background

McCune-Albright syndrome (MAS, OMIM#74800) is a rare and complex disease with an incidence of 1/1,000,000 to 1/100,000 (1). The pathogenesis of MAS is somatic gain-of-function mutations in the *GNAS* gene encoding the α -subunit of G protein (Gsa). The classic triad consists of café-au-lait skin macules, peripheral precocious puberty (PP), and fibrous dysplasia (FD), but this triad is only present in 24% of patients (2). As the Gsa protein is widely expressed across diverse tissues, the extent and severity of MAS manifestations depend on the embryonic timing of the postzygotic mutation and the degree of mosaicism across affected tissues. Therefore, MAS has a broad spectrum of clinical manifestations with high heterogeneity, posing challenges to its diagnosis and treatment (3).

Several cohort studies have been conducted abroad to explore the clinical features and outcomes of MAS, suggesting that clinical phenotypes and treatment responses may vary among patients of different ethnicities (4–7). However, most of the existing relevant studies on Chinese patients are small-sample case reports or single-center small cohort analyses, which have not yet fully summarized the clinical characteristics and treatment effects in large cohorts of Chinese MAS patients (8–10). Thus, comprehensive data specific to Chinese MAS patients are currently insufficient, failing to provide accurate and targeted references for Chinese clinicians in the diagnosis and treatment of MAS.

Based on the retrospective data of pediatric patients with MAS in our hospital, this study was intended to systematically clarify their clinical characteristics and treatment regimens, providing real-world evidence for clinical diagnosis and treatment.

Methods

Study Design and Participants

This single-center retrospective study enrolled children with MAS diagnosed in Beijing Children's Hospital (BCH) from Jan 14, 2016 to Jan 31, 2026. The diagnosis of MAS was based on the combination of FD and one or more extra skeletal feature, OR the presence of two or more extra skeletal features (café-au-lait skin macules, peripheral PP, thyroid lesions, growth hormone excess, neonatal hypercortisolism) (11).

This study was approved by the Ethics Committee of BCH.

Data collection

Clinical data at visit were collected from the medical records, including general information (gender, age, and height), clinical symptoms (café-au-lait skin macules, skeletal lesions, endocrine abnormalities, and other accompanying symptoms), laboratory examinations (hormone levels and genetic testing), imaging examinations (skeletal X-ray/CT/MRI and radionuclide bone scan), and treatment regimens (drug treatment and surgical treatment). Genetic testing of peripheral blood or affected tissue samples was performed using whole-exome sequencing.

Statistical analyses

Continuous variables were presented as mean $\pm$ SD or median (interquartile range) as appropriate, whereas categorical variables were presented as frequency (percentage). Differences between groups were analyzed using independent samples T test for normally distributed continuous data, Mann-Whitney U test for nonparametric continuous data, and χ^2 test for categorical variables. $P < 0.05$ was considered statistically significant at two-tailed tests. All statistical analyses were performed using IBM SPSS Statistical Software, version 31 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of enrolled pediatric patients with MAS

The clinical characteristics of 66 pediatric patients with MAS were described in Table 1. This study included 56 girls (84.8%) and 10 boys (15.2%), giving a sex ratio of 5.6:1. The median age at diagnosis was 5.18 years (range: 2 months to 15 years). Z score of height of the entire cohort was 0.61 (-0.02, 1.46). The most common signs were Café-au-lait skin macules and PP, both of which were found in 84.8% of patients. The chief complaint at presentation was most commonly related to PP (56/66, 84.8%), followed by FD (7/66, 10.6%). Females were predominantly admitted with chief complaints related to PP (55/56), whereas males most commonly presented with symptoms associated with FD or hypercortisolism (8/10). A total of 43 patients (65.1%) presented with a dyad of MAS features, 19 (28.8%) with a triad, and 4 (6.1%) with a tetrad. Only 14 patients (21.2%) manifested the classic triad of FD, café-au-lait macules, and PP.

Table 1
Clinical Characteristic in MAS Patients

Gender (female/male)	Patients with MAS (n = 66)	Female patients (n = 56)	Male patients (n = 10)	P value
	56/10	-	-	-
Age at diagnosis (years)	5.18 (3.75, 7.82)	5.11 (3.57, 7.78)	6.78 (4.24, 10.14)	0.317
Z score of height	0.61 (-0.02, 1.46)	0.83 (0.08, 1.47)	0.29 (-0.67, 0.95)	0.247
Café-au-lait skin macules, n (%)	56 (84.8)	49 (87.5)	7 (70.0)	0.169
Precocious puberty, n (%)	56 (84.8)	54 (96.4)	2 (20.0)	< 0.001*
Fibrous dysplasia, n (%)	35 (53.0)	26 (46.4)	9 (90.0)	0.015*
Thyroid lesions, n (%)	8 (12.1)	6 (10.7)	2 (20.0)	0.624
Hyperthyroidism, n (%)	5 (7.6)	4 (7.1)	1 (10.0)	0.573
Growth hormone excess, n (%)	1 (1.5)	0 (0.0)	1 (10.0)	0.152
Neonatal hypercortisolism, n (%)	2 (3.0)	0 (0.0)	2 (20.0)	0.021*
Dyad, n (%)	43 (65.1)	36 (64.3)	7 (70.0)	0.499
Triad, n (%)	19 (28.8)	16 (28.6)	3 (30.0)	1.000
Tetrad, n (%)	4 (6.1)	4 (6.1)	0 (0.0)	1.000
Classic triad, n (%)	14 (21.2)	14 (23.2)	0 (0.0)	0.104
Abbreviations: MAS, McCune-Albright syndrome.				
Classic triad: Fibrous dysplasia, café-au-lait macules, and precocious puberty.				
Data were presented as median (interquartile range).				
Significant <i>p</i> values (< 0.05) are presented with *.				

Precocious puberty

As shown in Table 1, a total of 56 patients (84.8%) presented with PP, with its incidence being significantly higher among female patients than male patients (96.4% vs. 20.0%, $p < 0.001$). The median age at onset of initial symptoms of PP was 3.75 years (range: 3 months to 8 years 1 month). Based on the GnRH stimulation test or basal gonadotropin and sex hormone measurement, 47 patients were classified as having peripheral PP, whereas the remaining 9 patients (8 female and 1 male) were

diagnosed with secondary central PP. Among 54 female patients with PP, unilateral or bilateral ovarian cysts were identified in 35 patients. A total of 4 patients underwent surgical intervention for ovarian masses. Among them, one patient underwent right oophorectomy before visit, and the other 3 patients received ovarian mass enucleation at an external hospital or our center. Postoperative pathological examinations confirmed that all lesions were ovarian cysts. The patient who underwent surgery at our institution developed ovarian torsion preoperatively. Among 47 patients with peripheral PP, 5 patients received letrozole, and 16 patients received tamoxifen after evaluation. Seven of the 9 patients with secondary central PP received GnRH analogue (GnRHa).

Fibrous dysplasia

Among 53.0% (35/66) of patients with FD, 91.4% (33/35) exhibit the polyostotic form. The incidence of FD was significantly higher among male patients than female patients (90.0% vs. 46.4%, $p = 0.015$). In terms of affected regions, the cranial bones were most frequently involved (24/35), followed by the lower limbs (19/35) and upper limbs (13/35). As shown in Fig. 1, the femur was the most commonly affected site (15/35) with the exception of the cranial bones, followed by the tibia (14/35) and humerus (11/35). The hands, feet, spine, ribs, and pelvis were less frequently involved. Eight patients presented with focal facial swelling attributable to craniofacial FD, and three patients sustained femoral shaft fractures caused by FD of the femur. Notably, CT imaging revealed optic canal stenosis in 4 patients with craniofacial FD, yet none exhibited obvious visual impairment. Five patients were treated with intravenous zoledronic acid, and one patient received oral alendronate sodium.

Café-au-lait skin macules

Café-au-lait skin macules affected 84.8% (56/66) of the cohort. Among patients with café-au-lait spots, the trunk was the most commonly affected site (35/56), followed by the lower extremities (21/56), head and neck (14/56), and upper extremities (9/56).

Thyroid lesions or hyperthyroidism

Eight patients exhibited abnormal findings on thyroid ultrasonography, characterized by diffuse thyroid parenchymal damage or single/multiple nodules. Hyperthyroidism occurred in 5 patients, who were treated with oral methimazole. There were no significant differences in the incidence of both conditions between male and female patients.

Hypercortisolism

Two infant patients were admitted due to the presence of Cushingoid features and growth retardation at 1 month after birth. Laboratory test revealed elevated serum cortisol and decreased adrenocorticotrophic hormone, while imaging examinations showed bilateral adrenal thickening. One patient underwent total left adrenalectomy followed by subtotal right adrenalectomy due to recurrent symptoms, with complete

resolution of symptoms postoperatively. The other patient experienced symptom recurrence after left adrenalectomy, while the parents declined further right adrenalectomy as well as medical therapy with steroidogenesis inhibitors.

Pituitary disease

One male patient aged 10 years and 11 months was identified with GH excess. He had been diagnosed with FD at an external hospital 6 years ago due to cranial asymmetry. On presentation, his height was 169cm (> 3SD), with right frontal-temporal prominence and absence of café-au-lait macules. Laboratory evaluation revealed elevated IGF-1 (531 ng/mL) and GH (11.304 ng/mL), with failure of GH suppression on glucose suppression testing. Prolactin was also elevated. Pituitary MRI demonstrated an enlarged pituitary gland with heterogeneous enhancement. Skeletal imaging confirmed multifocal craniofacial FD. Peripheral whole-exome sequencing did not identify any pathogenic mutation, and the parents declined any pharmacological treatment.

Genetic analysis

Of the 18 patients who underwent peripheral blood genetic testing, *GNAS* mutation (c.601C > A, p.Arg201Ser) was only detected in one patient. Genetic analysis of bone tissue obtained from bone biopsy was performed on three patients, all of whom harbored pathogenic *GNAS* mutations (c.601C > T, p.Arg201Cys or c.602G > A, p.Arg201His), which were undetectable in peripheral blood. Genetic testing of adrenal tissue obtained by adrenalectomy was undertaken in two patients. One patient carried a pathogenic *GNAS* mutation (c.602G > A, p.Arg201His), whereas the other patient exhibited a pathogenic *GNAS* mutation (c.602G > A, p.Arg201His) only on subsequent genetic analysis of skin tissue.

Discussion

In this retrospective study, we comprehensively characterized the clinical spectrum and treatment outcomes of 66 pediatric patients with MAS at a single center. PP and café-au-lait macules were the most common manifestations (84.8%), followed by FD (53.0%). Less frequent endocrinopathies included thyroid abnormalities (12.1%), neonatal hypercortisolism (3.0%), and GH excess (1.5%). The classic triad was present in only 21.2% of patients, with dyad presentations being predominant (65.1%). *GNAS* mutations were identified in all affected tissue samples but in only 5.6% of peripheral blood samples. These findings provide valuable epidemiological data for Chinese pediatric MAS patients and underscore the importance of comprehensive, long-term endocrine surveillance in this multisystem disorder.

In this study, the female-to-male ratio of MAS patients was 5.6:1, which was consistent with the female predominance reported in previous studies (2, 6). This female predominance has been attributed to the more overt clinical manifestations of peripheral PP in girls, which typically prompts earlier medical consultation and diagnosis. In contrast, boys with MAS often present with less conspicuous phenotypic features, potentially leading to underdiagnosis or delayed diagnosis. Nevertheless, in studies encompassing all age groups, FD and other endocrine disorders act as the primary diagnostic clues, resulting in a narrowed gender disparity (7).

PP was the most prevalent manifestation in our cohort (84.8%), with a striking female predominance (96.4% vs. 20.0%). The median age at onset of initial PP symptoms was 3.75 years, which was consistent with previous reports describing peripheral PP onset typically before age 4 years (12). Among patients with PP, the majority (83.9%) were classified as having peripheral PP, characterized by gonadotropin-independent activation of sex steroid production. The ovarian cysts identified in 35 female patients with PP represent the pathological consequence of constitutive Gsa activation in ovarian granulosa cells, leading to autonomous estrogen production independent of gonadotropin stimulation. Notably, 9 patients (16.1%) developed secondary central PP, a phenomenon well-documented in the literature where prolonged exposure to elevated sex steroids triggers premature activation of the hypothalamic-pituitary-gonadal axis. This transition from peripheral PP to central PP has important therapeutic implications, as it necessitates the addition of GnRHa to the treatment regimen. The recognition of this central PP progression underscores the importance of regular monitoring of gonadotropin levels in MAS patients with peripheral PP to guide appropriate therapeutic interventions.

FD was documented in 53.0% of our cohort, with a significantly higher prevalence in male patients (90.0% vs. 46.4%). This gender difference in FD prevalence within our cohort contrasts with population-based studies demonstrating equal FD incidence between males and females (7). The apparent discrepancy may reflect diagnostic bias: females with MAS are more likely to present with PP as the chief complaint, whereas males more commonly come to medical attention due to FD, leading to a higher proportion of FD in male MAS patients within clinical cohorts. The polyostotic form predominated in our cohort (91.4%), consistent with the established association between MAS and extensive skeletal disease. Craniofacial bones were the most frequently affected site (68.6%), which may lead to facial asymmetry, cranial nerve compression, and cosmetic deformities. Notably, although imaging examinations in our cohort revealed optic canal stenosis in patients with craniofacial FD, none of them experienced obvious visual impairment. This finding was consistent with the landmark study demonstrating that majority of FD patients with optic canal narrowing maintained normal vision and prophylactic optic nerve decompression was not indicated in asymptomatic patients (13). Nevertheless, regular monitoring of visual acuity and visual fields remains essential for early detection of potential optic nerve compromise. The femoral involvement observed in 15 patients, with 3 sustaining femoral shaft fractures, exemplified the substantial morbidity associated with FD. The management of FD with bisphosphonates (zoledronic acid in 5 patients, alendronate in 1 patient) reflected current practice aimed at reducing bone pain and lowering bone turnover markers, although evidence regarding the efficacy of antiresorptive therapy in FD remains heterogeneous across studies (14, 15). It has been recommended that clinicians should limit bisphosphonate use to the lowest dose and interval needed to control pain and make efforts to reduce dental risks (3, 11).

Café-au-lait skin macules were observed in 84.8% of patients, representing one of the most consistent clinical features of MAS (16). The characteristic distribution pattern, with the trunk being the most commonly affected site (62.5%), followed by the lower extremities (37.5%), aligns with classical descriptions of MAS-associated pigmented lesions (17). These hyperpigmented macules typically exhibit irregular and jagged borders, distinguishing them from the smooth-bordered café-au-lait spots

seen in neurofibromatosis type 1. The high prevalence of café-au-lait macules in our cohort underscores their diagnostic utility, as they are often the earliest clinical sign of MAS and may precede the development of endocrine or skeletal manifestations by several years. Clinicians should maintain a high index of suspicion for MAS when evaluating patients with atypical café-au-lait skin macules, particularly those with irregular borders or unilateral distribution.

Thyroid abnormalities were less prevalent in our cohort compared to previous reports, with ultrasonographic abnormalities detected in 12.1% of patients and hyperthyroidism in 7.6%, versus reported rates of 31–66% for thyroid abnormalities and approximately 30% for hyperthyroidism in previous studies (16, 18). This discrepancy may be attributed to the relatively young age of our cohort (median age 5.18 years), as the reported mean age at onset of thyroid disease in MAS is approximately 10.8 years (18). All patients with hyperthyroidism in this study were managed with methimazole, which effectively controls symptoms by inhibiting thyroid hormone synthesis. Regular thyroid function monitoring is recommended for all MAS patients, as thyroid dysfunction can significantly impact growth, development, and overall health outcomes.

As the rarest endocrine abnormalities of MAS (19), neonatal hypercortisolism was exclusively confirmed in two male patients in our cohort. This rare but potentially life-threatening manifestation of MAS results from constitutive *Gsa* activation and persistent cAMP signaling in cells of the fetal adrenal zone caused by *GNAS* mutation, which drives autonomous ACTH-independent cortisol hypersecretion. The two infants in our cohort presented with Cushingoid features and growth retardation within the first month of life, highlighting the importance of early recognition and intervention. Since the fetal adrenal zone normally undergoes involution during the first months of life, this temporal window explains both the exclusive neonatal onset and the potential for spontaneous resolution in one third of cases (19, 20). Medical management with steroidogenesis inhibitors such as metyrapone should be considered as initial therapy, particularly in critically ill neonates who may not tolerate surgery or in patients with concurrent cholestatic hepatitis where ketoconazole is contraindicated due to hepatotoxicity, and may serve as a bridge while awaiting potential spontaneous resolution (21). However, bilateral adrenalectomy remains the definitive treatment for persistent and severe hypercortisolism (22), as unilateral adrenalectomy is insufficient due to the bilateral adrenal involvement inherent to MAS, as evidenced by the recurrence in our patients after unilateral intervention (19, 23).

Genetic analysis in our cohort demonstrated a remarkably low detection rate of *GNAS* mutation in peripheral blood (1/18, 5.6%), which is consistent with the known somatic mosaic nature of the disease (3). The mutation burden in peripheral blood is often below the detection threshold of conventional Sanger sequencing including whole-exome sequencing due to the postzygotic origin of *GNAS* mutation and variable tissue distribution (23). In contrast, *GNAS* mutations were identified in all three bone tissue samples and adrenal or skin tissue sample analyzed, supporting the recommendation that genetic testing should be performed on affected tissues when feasible (24). These findings emphasized the limitations of peripheral blood testing by whole-exome sequencing, which yielded near-zero detection rates, whereas allele-enrichment PCR strategies and digital droplet PCR could substantially improve the

detection rate to approximately 38%-58% in whole blood and up to 68%-80% in circulating cell-free DNA (25–27). The most commonly identified mutations were at codon 201 (p.Arg201Cys and p.Arg201His), consistent with the well-established mutational hotspot of *GNAS* in MAS (28).

The clinical heterogeneity of MAS presents significant challenges for clinicians involved in the diagnosis and management of these patients. The broad spectrum of clinical manifestations in MAS arises from the timing of the somatic *GNAS* mutation during embryonic development and the distribution of affected tissues in the mosaic state. Earlier postzygotic mutations that occur during earlier developmental stages result in more widespread involvement, whereas later mutations lead to more restricted phenotypic expression. In our cohort, only 21.2% of patients manifested the classic triad of FD, café-au-lait macules, and PP concurrently, consistent with prior reports that the complete triad occurred in approximately 24% of MAS patients (2). This observation underscores that the diagnosis of MAS should not rely solely on the presence of the complete triad, any combination of characteristic features warrants clinical suspicion and appropriate evaluation.

This study has some limitations. First, the single-center retrospective design inherently introduced potential bias and limited the availability of standardized follow-up data. Second, the limited sample size, particularly the small number of male patients and patients with rare manifestations, may restrict the statistical power for detecting certain associations and limit the generalizability of gender-specific findings. Third, genetic testing was not uniformly performed across all patients, and the majority of patients did not undergo tissue-based molecular analysis. Fourth, long-term follow-up data on treatment outcomes were not systematically collected, limiting our ability to assess the effectiveness of various therapeutic interventions. Future prospective multicenter studies with standardized protocol and long-term follow-up are needed to validate our findings.

Conclusions

This study represents the largest single-center retrospective cohort detailing the clinical profile of Chinese pediatric MAS patients. The clinical spectrum of MAS in Chinese pediatric patients largely parallels that of Western cohorts, yet notable differences in manifestation prevalence likely reflect referral patterns and the younger age of our cohort. Given the rarity of the classic triad, incomplete presentations should prompt timely diagnostic evaluation. Longitudinal surveillance for late-onset endocrinopathies and adoption of tissue-based or highly sensitive genetic testing are imperative for optimizing outcomes.

Abbreviations

MAS

McCune-Albright syndrome

FD

fibrous dysplasia

PP

peripheral precocious puberty

Gsa

α -subunit of G protein

BCH

Beijing Children's Hospital

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of our hospital.

Consent for publication

Not applicable. Consent signed by patient's parents at hospital admission, allows to use any personal data in anonymous form for publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contribution

All authors have contributed significantly and in keeping with the latest guidelines of the International Committee of Medical Journal Editors. Conception or design: D.W. and J.Y. conceptualized this study. X.N., Y.D., L.W., M.Q, X.M., L.L., X.L., Q.W., C.S., M.L., W.L., J.Y., and D.W. performed data acquisition and analysis. X.N., J.Y., and D.W. drafted the manuscript. All authors contributed to critical revision of the manuscript.

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Figures

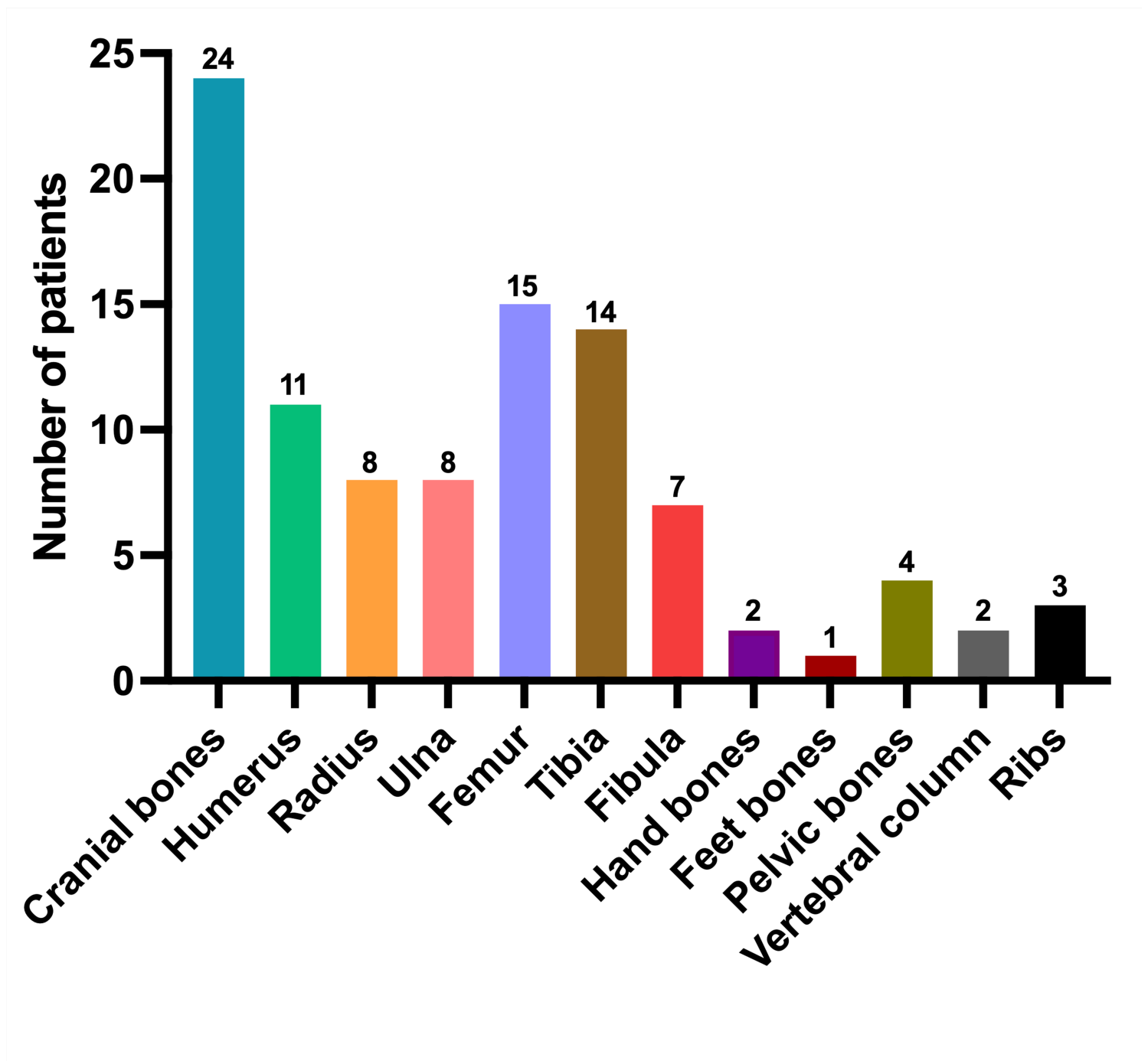


Figure 1

Distribution of fibrous dysplasia across skeletal sites in 35 patients with McCune-Albright syndrome.