Clinical, Cosmetic and Investigational Dermatology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Characteristics of Multiple Café-Au-Lait Macules and Their Potential Significance in the Early Screening of Genetic Diseases

Tong Chen[1–3], Jiamin Wu[1], Xin Yang[2], Zhikuan Xia[1,2], Rongya Yang[1,2]

[1]The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, 510515, People's Republic of China; [2]Department of Dermatology, The Seventh Medical Center of Chinese PLA General Hospital, Beijing, 100080, People's Republic of China; [3]Department of Dermatology, Longgang Central Hospital, Shenzhen, Guangdong, 518116, People's Republic of China

Correspondence: Rongya Yang, Email drYangRongya@outlook.com; yangrya@sina.com; Zhikuan Xia, Email drXiaZhikuan@outlook.com; sum7@sina.com

Background: Café-au-lait macules (CALMs) are common skin manifestations, and their number and distribution may indicate potential genetic disorders, such as Neurofibromatosis Type 1 (NF1). This study aimed to investigate the clinical characteristics of multiple CALMs and their significance in the early screening of genetic disorders.

Methods: This retrospective study included 98 patients diagnosed between May 2021 and May 2024 in two hospitals. Patients were divided into three groups based on the number of CALMs and whether other skin manifestations were present: Group 1 (≥ 6 CALMs with other skin manifestations), Group 2 (≥ 6 CALMs without other skin manifestations), and Group 3 (< 6 CALMs without other skin manifestations). Detailed clinical evaluations and imaging examinations were conducted to record the number, size, distribution of CALMs, and associated symptoms. Multivariate logistic regression analysis was performed to explore the relationship between CALMs and other systemic symptoms.

Results: Group 1 patients showed significantly higher incidences of neurological symptoms (eg, neurofibromas 54%, $P < 0.001$) and skeletal system symptoms (eg, bone deformities 38%, $P = 0.001$) compared to Groups 2 and 3. Imaging examinations revealed an abnormality rate of 90% in Group 1 ($P < 0.001$). Logistic regression analysis indicated that the number of CALMs (≥ 10) was significantly associated with neurological (OR = 7.664, $P = 0.001$) and skeletal system symptoms (OR = 4.623, $P = 0.014$). The distribution of CALMs on the face and neck also showed a certain influence on symptoms.

Conclusion: The number and distribution of CALMs are significant in the early screening of genetic diseases, particularly in identifying patients with potential neurological and skeletal system abnormalities.

Keywords: café-au-lait macules, neurofibromatosis type 1, genetic disorders, early screening

Introduction

Café-au-lait macules (CALMs) are common pigmented skin lesions characterized by smooth, well-demarcated macules ranging from light brown to dark brown.[1,2] While generally benign, they can serve as markers for potential genetic disorders, particularly neurocutaneous syndromes such as neurofibromatosis type 1 (NF1).[3,4] NF1 is an autosomal dominant genetic disorder caused by mutations in the NF1 gene and is one of the most well-documented diseases associated with CALMs.[5] Early identification of patients at risk of genetic disorders based on CALM characteristics can significantly improve disease management and prognosis, particularly in preventing complications such as skeletal deformities and central nervous system (CNS) abnormalities.[6]

The diagnostic significance of CALMs in NF1 has been extensively studied. One of the diagnostic criteria for NF1 is the presence of six or more CALMs, with each macule exceeding 0.5 cm in diameter in prepubertal individuals or ≥ 1.5 cm in adults.[7] Studies have shown that the number and distribution of CALMs are associated with the severity of NF1-related complications, including neurofibromas, skeletal abnormalities, and learning disabilities.[8,9] Furthermore, CALMs located on the face and neck are more likely to be associated with CNS manifestations, such as optic pathway

Received: 6 February 2025
Accepted: 17 May 2025
Published: 30 May 2025

gliomas and hydrocephalus.[10,11] While NF1 is the most common genetic disorder associated with CALMs, other syndromes, such as McCune-Albright syndrome, Legius syndrome, and tuberous sclerosis complex, may also present with similar skin manifestations.[10,12] Differentiating these conditions is crucial due to their varying systemic involvement and prognoses. Additionally, sporadic CALMs occur in the absence of genetic susceptibility, typically as isolated lesions without systemic associations.[13,14]

Given the potential clinical significance of CALMs, incorporating their characteristics into early genetic disease screening programs can improve diagnostic accuracy. Studies suggest that CALM features, particularly their number and distribution, can serve as non-invasive screening markers for identifying patients at risk of genetic syndromes.[13,15] Imaging techniques such as MRI further elucidate the relationship between CALMs and systemic abnormalities, with manifestations like neurofibromas and skeletal deformities being common in patients with extensive CALMs.[16]

Although the link between CALMs and genetic disorders has been established, systematic analyses of CALM clinical features across different patient populations remain limited. Moreover, the predictive value of CALM distribution and size in identifying systemic abnormalities has not been fully explored. This study follows a retrospective design, analyzing data from patients diagnosed between May 2021 and May 2024 in two hospitals. The retrospective design allows us to utilize existing patient records to explore the relationship between CALM characteristics and associated systemic symptoms, without the need for new data collection or interventions. This approach efficiently identifies patterns and trends that can inform genetic disease screening, particularly for genetic disorders such as NF1.

This study aims to evaluate the clinical and pathological characteristics of CALMs in patients with or without associated skin manifestations, with a focus on their significance in early screening for genetic diseases. By employing detailed clinical evaluations and imaging studies, this research seeks to enhance the understanding of CALMs as early screening markers for genetic diseases, particularly NF1, and to lay the groundwork for future diagnostic guidelines.

Methods

Study Design and Population

This study is a retrospective analysis conducted from May 2021 to May 2024. The cases were sourced from the Department of Dermatology at the Seventh Medical Center of Chinese PLA General Hospital and Longgang Central Hospital. A total of 98 patients were included in the study, which was approved by the ethics committees of the Seventh Medical Center of Chinese PLA General Hospital and Longgang Central Hospital. This study was conducted in accordance with the Declaration of Helsinki. All subjects signed the consent form before participation in the study. Consent form was obtained from the legal guardians of all underage participants prior to their involvement in the study. The ages of all patients ranged from 8 to 60 years, and they all provided complete medical histories and imaging data. The inclusion criteria involved patients with multiple CALMs (≥ 6) or isolated CALMs (< 6). Exclusion criteria included incomplete data, insufficient follow-up, patients with other inflammatory or secondary skin diseases, and those with serious systemic diseases that could potentially affect the study results. Based on the number of CALMs and associated manifestations, the study population was divided into three groups: Group 1 ($n = 39$) had multiple CALMs (≥ 6), with other skin manifestations (such as freckles, skin fibromas, etc).; Group 2 ($n = 32$) had multiple CALMs (≥ 6) but without other skin manifestations; and Group 3 ($n = 27$) had isolated CALMs (< 6), with no clear etiology. This study ensured the representativeness of the study subjects and data integrity through strict inclusion and exclusion criteria.

Clinical Evaluation

All study participants will undergo a detailed clinical evaluation. First, the physician will conduct a physical examination of the patients' CALMs, recording their number, distribution, color, and other characteristics. To measure the size of each CALM, a caliper will be used to determine its longest diameter in millimeters. The color of CALMs will be assessed visually and categorized as light brown and dark brown. A standardized color scale will be referenced to reduce subjective differences in color interpretation. The presence of other skin manifestations such as freckles, skin fibromas, skin folds, and pigment loss will also be evaluated. Additionally, the physician will assess whether the patients have any systemic symptoms, particularly related to the nervous and skeletal systems (such as neurofibromas, skeletal deformities,

etc). For patients with a family history of genetic diseases, the presence of hereditary conditions such as neurofibromatosis and xeroderma pigmentosum will be documented.

Imaging Examination

All patients will undergo a full-body MRI scan to assess abnormalities in the nervous and skeletal systems. The neurological examination will include brain scans, focusing on lesions such as neurofibromas and hydrocephalus. The skeletal system examination will cover the spine, limbs, and long bones, primarily looking for skeletal deformities and bone fibromas. The scanning will use multi-planar sequences (such as T1, T2-weighted imaging) combined with contrast-enhanced scans to improve lesion visibility. Experienced radiologists in accordance with standardized criteria will interpret all imaging results.

Statistical Analysis

All data analyses were performed using SPSS 25.0 software. Continuous variables were expressed as mean ± standard deviation (SD), and inter-group differences were analyzed using independent sample t-tests or Mann–Whitney *U*-tests. Categorical variables were described by frequency and composition ratios, and inter-group comparisons were conducted using chi-square tests or Fisher's exact tests. Additionally, logistic regression analysis was used to calculate odds ratios (OR) and their 95% confidence intervals (95% CI) to explore the relationship between the number, size, and distribution of CALMs and systemic symptoms, and to evaluate the clinical significance of the screening model. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Results

Clinical and Pathological Characteristics of Patients

This study included 98 patients, and Table 1 summarizes the clinical and pathological characteristics of the three groups. Group 1 (n = 39) had an average age of 25.8 ± 8.2 years, with a higher rate of positive family history (31%). In terms of ethnicity, Group 1 had a majority of Han (94.87%) and a minority of Minority (5.13%). Regarding region, Group 1 had 23 patients from urban areas and 16 from rural areas. Among these patients, 64% had ≥ 10 CALMs, and most had dark brown spots (72%) and large areas (> 15 cm², 38%). Group 2 (n = 32) had an average age of 24.3 ± 7.5 years, with a family history rate of 19%. Among these patients, 50% had ≥ 10 CALMs and 50% had between 6 and 10 spots, with most spots being dark brown (63%). Group 3 (n = 27) had the youngest average age (21.5 ± 6.9 years), and light brown CALMs (70%) predominated. All patients in this group had fewer than 6 spots. In groups 1 and 2, CALMs were primarily located on the face and neck, while in group 3, they were more frequently found on the limbs. Overall, patients in group 1 exhibited stronger features of genetic disease, particularly in terms of the number, color, and associated symptoms of CALMs, highlighting their significance as clinical indicators for early genetic disease screening.

Analysis of Clinical Manifestations and Imaging Examination Results

Table 2 and Figure 1 show the incidence of neurological and skeletal system symptoms in different groups. Group 1 had a significantly higher incidence of neurological and skeletal system symptoms compared to group 2 and group 3. Specifically, the incidence of neurofibromas in group 1 was 38%, much higher than 25% in group 2 and 4% in group 3 (P = 0.005). Additionally, group 1 exhibited higher incidences of hydrocephalus (13%) and intellectual disability (10%), while group 2 and group 3 had relatively lower rates with no significant differences (P = 0.166, P = 0.580). In terms of skeletal symptoms, the incidence of bone deformities (38%) and osteofibromas (21%) in group 1 was also significantly higher than in Group 2 (25%, 13%) and group 3 (0%) (P = 0.001, P = 0.044). Imaging results (Table 3 and Figure 2) further supported these clinical findings. Group 1 had an imaging abnormality rate of 90%, indicating that most patients had abnormalities in the neurological or skeletal systems, whereas the abnormality rates in group 2 and group 3 were 31% and 7%, respectively (P < 0.001). These data suggest that patients in group 1 are more likely to have neurological and skeletal abnormalities related to genetic diseases, especially symptoms like neurofibromas, hydrocephalus, and osteofibromas, which are consistent with the features of diseases such as Neurofibromatosis Type 1 (NF1). In contrast, imaging abnormalities were less common in

Table 1 Basic Characteristics of Patients

Characteristics	Group 1 (n = 39)	Group 2 (n = 32)	Group 3 (n = 27)	*P*
Age (mean ± SD)	25.8 ± 8.2	24.3 ± 7.5	21.5 ± 6.9	0.084
Race				>0.999
Han	37 (94.87%)	31 (96.87%)	26 (96.30%)	
Minority	2 (5.13%)	1 (3.13%)	1 (3.7%)	
Region				0.430
Urban	23	16	18	
Rural	16	16	9	
Sex				0.064
Male (%)	22 (56%)	20 (63%)	9 (33%)	
Female (%)	17 (44%)	12 (37%)	18 (67%)	
Family history				0.066
Yes	12 (31%)	6 (19%)	2 (7%)	
No	27 (69%)	26 (81%)	25 (93%)	
CALM count				< 0.001
≤ 6 (%)	0 (%)	0 (%)	27 (100%)	
6–10 (%)	14 (36%)	16 (50%)	0 (%)	
≥ 10 (%)	25 (64%)	16 (50%)	0 (%)	
Distribution				
Face and neck (%)	24 (62%)	20 (63%)	10 (37%)	0.085
Trunk (%)	10 (26%)	8 (25%)	8 (30%)	0.911
Limbs (%)	5 (12%)	4 (12%)	9 (33%)	0.062
Area of CALMs				
Small: 3–9 cm^2	10 (26%)	12 (38%)	8 (30%)	0.554
Medium: 9–15 cm^2	14 (36%)	14 (44%)	11 (41%)	0.903
Large: >15 cm^2	15 (38%)	6 (19%)	8 (30%)	0.279
CALM color				0.002
Dark brown (%)	28 (72%)	20 (63%)	8 (30%)	
Light brown (%)	11 (28%)	12 (37%)	19 (70%)	

Table 2 The Incidence of Neurological and Skeletal System Symptoms in Different Groups

Clinical Symptoms	Group 1 (n = 39)	Group 2 (n = 32)	Group 3 (n = 27)	*P*
Neurofibroma	15 (38%)	8 (25%)	1 (4%)	0.005
Hydrocephalus	5 (13%)	3 (9%)	0 (0%)	0.166
Intellectual disability	4 (10%)	2 (6%)	1 (4%)	0.580
Other neurological symptoms	4 (10%)	2 (6%)	0 (0%)	0.232
Bone deformities	15 (38%)	8 (25%)	0 (0%)	0.001
Osteofibroma	8 (21%)	4 (13%)	0 (0%)	0.044
Scoliosis	3 (8%)	2 (6%)	0 (0%)	0.354
Other skeletal system symptoms	3 (8%)	2 (6%)	0 (0%)	0.354

Groups 2 and 3, indicating that these patients may have milder symptoms or not exhibit clear genetic disease features. The underlying causes of these differences, including the potential interaction between genetic and environmental factors, warrant further investigation to fully understand their contribution to these disparities. In summary, these findings underscore the clinical significance of CALMs in identifying patients at risk for genetic disorders, particularly those with neurological and skeletal abnormalities, and highlight the importance of using CALMs as an early diagnostic tool in genetic disease screening.

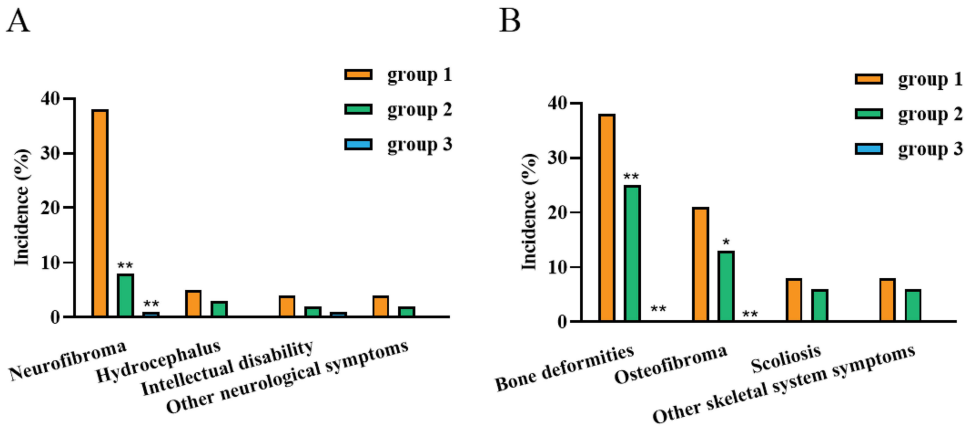

Figure 1 Incidence of neurological symptoms (**A**) and skeletal symptoms (**B**) in patients from different groups. *p < 0.05, **p < 0.01, compared to group 1.

The Association Analysis Between CALMs Characteristics and Symptoms Related to Genetic Diseases

Figure 3 presents the results of a multivariate logistic regression analysis examining the relationship between the number, size, distribution of CALMs, and other clinical characteristics with neurological and skeletal system symptoms. According to the results, the number of CALMs (especially ≥10) was significantly associated with the occurrence of neurological symptoms, with an odds ratio (OR) of 7.664 (95% CI: 2.257–26.020, P = 0.001), indicating that patients with ≥10 CALMs had a higher risk of developing neurological symptoms. Similarly, the number of CALMs (≥10) was also significantly associated with the occurrence of skeletal system symptoms, with an OR of 4.623 (95% CI: 1.264–15.672, P = 0.014). Additionally, the distribution of CALMs (especially on the face and neck) had some influence on the relationship with neurological and skeletal system symptoms, although some variables showed slightly higher P-values, suggesting a possible impact on symptom occurrence. In summary, these findings support the importance of CALM quantity and distribution in predicting neurological and skeletal symptoms, making them crucial markers for early genetic disease screening, particularly in identifying systemic abnormalities.

Discussion

CALMs are benign pigmented skin lesions increasingly recognized as potential biomarkers for genetic diseases, particularly neurocutaneous syndromes such as NF1.[17,18] This study underscores the importance of CALM characteristics (eg, number, size, and distribution) as clinical indicators in the early screening of genetic disorders. Our findings highlight the significant associations between CALM features and systemic abnormalities, particularly in the nervous and skeletal systems, reinforcing their diagnostic utility.

The data revealed that group 1 patients exhibited significantly higher rates of neurological and skeletal abnormalities compared to groups 2 and 3. Neurological manifestations in group 1, including neurofibromas (54%) and hydrocephalus (13%), align with NF1 diagnostic criteria and corroborate prior research emphasizing the diagnostic value of CALMs in NF1 screening. This is consistent with previous studies, which also highlight the importance of CALM features, such as quantity and distribution, in early NF1 diagnosis. However, while those studies focused on the general correlation between CALMs and systemic symptoms, our research specifically emphasizes the predictive value of having ≥ 10 CALMs as a reliable indicator of neurological and skeletal abnormalities. This distinction provides additional insights

Table 3 The Imaging Findings of Different Groups

Clinical Symptoms	Group 1 (n = 39)	Group 2 (n = 32)	Group 3 (n = 27)	*P*
Imaging abnormalities (Neurological/Skeletal system)	35 (90%)	10 (31%)	2 (7%)	< 0.001
Imaging normal findings	4 (10%)	22 (69%)	25 (93%)	< 0.001

https://doi.org/10.2147/CCID.S521076

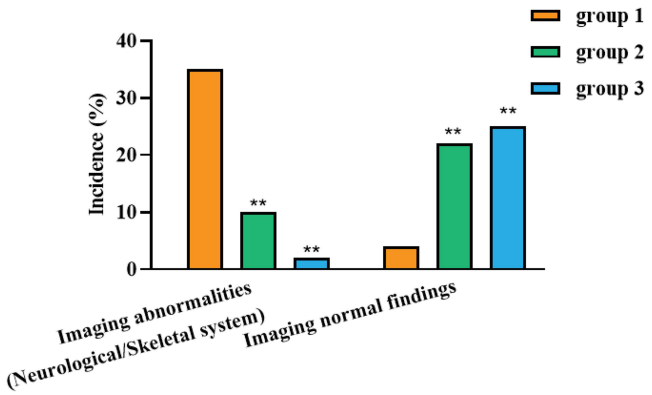

Figure 2 The imaging findings of different groups. **p < 0.01, compared to group 1.

into the use of CALMs as a diagnostic tool in genetic disease screening.[19,20] Additionally, skeletal abnormalities such as deformities (38%) and osteofibromas (21%) further substantiate the strong correlation between CALM characteristics and the pathophysiology of genetic disorders. Our results also indicate that CALM quantity (≥ 10) is a reliable predictor of neurological and skeletal symptoms, with OR of 7.664 and 4.623, respectively. For example, earlier researches have found correlations between CALMs and neurofibromas, but our study uniquely emphasizes the predictive value of CALM quantity in forecasting systemic abnormalities, offering a refined diagnostic approach. Moreover, the anatomical distribution of CALMs, particularly on the face and neck, was linked to an increased risk of central nervous system (CNS) abnormalities, such as optic gliomas and brainstem lesions. Although certain variables exhibited limited statistical significance, these observations underscore the importance of comprehensive clinical evaluations and imaging for patients with extensive CALMs.

Interestingly, compared to group 1, group 2 showed a lower prevalence of systemic abnormalities. This distinction highlights the additional diagnostic value of accompanying skin findings, such as freckles and cutaneous neurofibromas, which are hallmark features of NF1. Conversely, group 3, characterized by isolated or few CALMs, exhibited minimal systemic involvement, suggesting that isolated CALMs are more likely sporadic and benign.[21] Imaging played a crucial role in identifying systemic abnormalities, with MRI revealing a 90% abnormality rate in group 1 patients. This supports integrating imaging techniques into the early diagnostic workflow for patients with extensive CALMs, particularly in the presence of additional risk factors. Furthermore, advanced imaging modalities, such as contrast-enhanced MRI can enhance the detection of subtle lesions and help differentiate NF1 from other genetic syndromes, such as Legius syndrome and McCune-Albright syndrome.[22]

Despite its strengths, this study has certain limitations. First, the absence of genetic screening might have led to misdiagnoses or missed diagnoses in some cases. Since genetic mutations, particularly in the NF1 gene, are established diagnostic markers, future studies incorporating genetic testing could validate and improve the accuracy of screening models.[21,23] Additionally, the retrospective design and relatively small sample size may limit the generalizability of the findings. Prospective studies with larger cohorts and standardized protocols could further elucidate the associations observed in this study.

In conclusion, this study reinforces the clinical significance of CALM characteristics in the early screening of genetic diseases. By leveraging CALM features, along with detailed clinical evaluations and imaging findings, clinicians can improve the early detection and management of conditions such as NF1. Integrating genetic testing into future research and clinical protocols could further optimize diagnostic accuracy and patient outcomes.

Conclusion

This study highlights the clinical significance of CALMs as markers for early genetic disease screening, particularly for NF1. The findings demonstrate that CALM quantity (≥ 10), distribution, and associated skin features are closely linked to systemic abnormalities in the nervous and skeletal systems. Incorporating CALM evaluation into early diagnostic

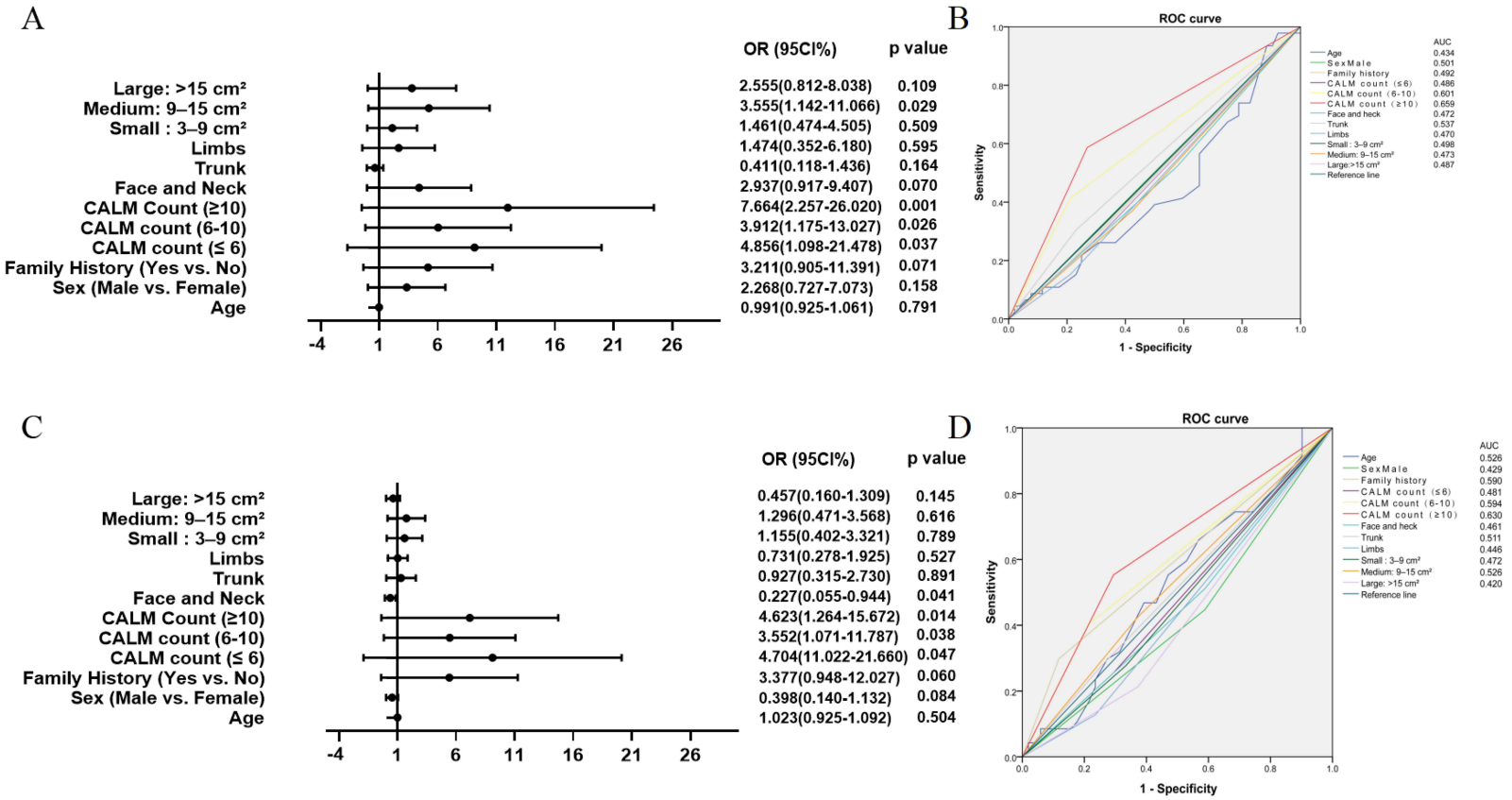

Figure 3 Multivariate logistic regression analysis of CALMs characteristics and genetic disease-related symptoms. (**A**) Multivariate logistic regression analysis for the association between CALMs characteristics and neurological symptoms, showing odds ratio (OR) with 95% confidence intervals (CIs) and corresponding p-values. (**B**) Receiver operating characteristic (ROC) curves illustrating the diagnostic performance for neurological symptoms, with area under the curve (AUC) values displayed for each parameter. (**C**) Multivariate logistic regression analysis for skeletal system symptoms, displaying OR, 95% CIs, and p-values. (**D**) ROC analysis evaluating the diagnostic performance for skeletal system symptoms, with AUC values for each characteristic or factor. The results suggest that specific CALMs characteristics are associated with neurological and skeletal symptoms, demonstrating moderate diagnostic accuracy.

https://doi.org/10.2147/CCID.S521076

protocols, supplemented with imaging technologies, holds promise for improving the early detection and management of genetic diseases.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of the Seventh Medical Center of Chinese PLA General Hospital and Longgang Central Hospital. All subjects signed the consent form before participation in the study. Consent form was obtained from the legal guardians of all underage participants prior to their involvement in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study did not receive any funding in any form.

Disclosure

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1. Shah A, Hawryluk EB, Seiverling EV. Dermoscopy aids in differentiating café-au-lait macules from congenital melanocytic nevi in patients with darker skin phototypes. *Pediatric Dermatol*. 2024;2024:1. doi:10.1111/pde.15697
2. Fernandez JK, Guo EL, Richmond H, Friedman PM. The 730 nm picosecond titanium sapphire laser for treatment of café-au-lait macules in all skin types. *Lasers Surg Med*. 2024;56(3):257–262. doi:10.1002/lsm.23769
3. Lovatt C, Williams M, Gibbs A, et al. Pigment epithelium derived factor drives melanocyte proliferation and migration in neurofibromatosis café au lait macules. *Skin Health Dis*. 2024;4(5):e394. doi:10.1002/ski2.394
4. Galasso C, Casarelli L, El Malhany N, et al. Presence of neurologic signs in children with neurofibromatosis type 1. *Minerva pediatrics*. 2023;75 (1):1–7. doi:10.23736/s2724-5276.16.04476-5
5. Jha SK, Mendez MD. *Cafe Au Lait Macules*. StatPearls Publishing; 2025.
6. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics*. 2000;105(3 Pt 1):608–614. doi:10.1542/peds.105.3.608
7. Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. *Genet Med*. 2021;23(8):1506–1513. doi:10.1038/s41436-021-01170-5
8. Friedman JM, Birch PH. Type 1 neurofibromatosis: a descriptive analysis of the disorder in 1,728 patients. *Am J Med Genet*. 1997;70(2):138–143. doi:10.1002/(sici)1096-8628(19970516)70:2<138::aid-ajmg7>3.0.co;2-u
9. Kang E, Yoon HM, Lee BH. Neurofibromatosis type I: points to be considered by general pediatricians. *Clin Experiment Pediatr*. 2021;64 (4):149–156. doi:10.3345/cep.2020.00871
10. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet*. 2007;44(2):81–88. doi:10.1136/jmg.2006.045906
11. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. *Genet Med*. 2010;12(1):1–11. doi:10.1097/GIM.0b013e3181bf15e3
12. Pasmant E, Sabbagh A, Hanna N, et al. SPRED1 germline mutations caused a neurofibromatosis type 1 overlapping phenotype. *J Med Genet*. 2009;46(7):425–430. doi:10.1136/jmg.2008.065243
13. Denayer E, Legius E. Legius Syndrome and its Relationship with Neurofibromatosis Type 1. *Acta Dermato-Venereol*. 2020;100(7):adv00093. doi:10.2340/00015555-3429
14. Suerink M, Potjer TP, Versluijs AB, et al. Constitutional mismatch repair deficiency in a healthy child: on the spot diagnosis? *Clin Genet*. 2018;93 (1):134–137. doi:10.1111/cge.13053
15. Landau M, Krafchik BR. The diagnostic value of café-au-lait macules. *J Am Acad Dermatol*. 1999;40(6 Pt 1):877–890. doi:10.1016/s0190-9622(99)70075-7
16. Sabry AO, Abolenain AS, Mostafa N, Ramadan A, Ghanem M. Jaffe-Campanacci syndrome; a case series and review of the literature. *BMC Musculoskeletal Disorder*. 2024;25(1):502. doi:10.1186/s12891-024-07581-0

17. Horn S, Neuhann T, Hennig C, et al. LZTR1 loss-of-function variants associated with café au lait macules with or without freckling. *Front Neurol*. 2024;15:1391425. doi:10.3389/fneur.2024.1391425
18. Ferrito N, Báez-Flores J, Rodríguez-Martín M, et al. Biomarker Landscape in RASopathies. *Int J Mol Sci*. 2024;25(16):8563. doi:10.3390/ijms25168563
19. Farschtschi S, Mautner VF, McLean ACL, Schulz A, Friedrich RE, Rosahl SK. The Neurofibromatoses. *Deutsches Arzteblatt Int*. 2020;117(20):354–360. doi:10.3238/arztebl.2020.0354
20. Anderson S. Café au Lait Macules and Associated Genetic Syndromes. *J Pediatric Healthcare*. 2020;34(1):71–81. doi:10.1016/j.pedhc.2019.05.001
21. Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated Approach to Patients with Multiple Café au Lait Macules. *Dermatol Clin*. 2022;40(1):9–23. doi:10.1016/j.det.2021.08.002
22. Van Es S, North KN, McHugh K, De Silva M. MRI findings in children with neurofibromatosis type 1: a prospective study. *Pediatric Radiol*. 1996;26(7):478–487. doi:10.1007/bf01377205
23. Kehrer-Sawatzki H, Cooper DN. Challenges in the diagnosis of neurofibromatosis type 1 (NF1) in young children facilitated by means of revised diagnostic criteria including genetic testing for pathogenic NF1 gene variants. *Hum Genet*. 2022;141(2):177–191. doi:10.1007/s00439-021-02410-z