REVIEW ARTICLE

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Craniofacial findings in syndromes associated with cafe-au-lait spots: a literature review

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INTRODUCTION

Cafe-au-lait spots (CALS), also called cafe-au-lait macules, are uniformly pigmented light to dark brown spots on the skin that may be present at birth or develop in childhood[1]. They usually appear as light brown in light-skinned people and medium to dark brown in dark-skinned people. The size of the spots can vary from 1–2 mm up to >20 cm^2. Morphologically, CALS are more frequently oval-shaped and have smooth edges, although other formats are described[3].

Histologically, an increase in melanin content has been demonstrated in both melanocytes and basal keratinocytes, and in some pathological conditions, an increase in the number of melanocytes, although proliferation of melanocytes is not seen[2]. CALS can occur anywhere in the body with the exception of the scalp, palms, and plantae, but they appear more frequently on the trunk and extremities, and less commonly on the face[4].

Several steps are involved in determining the color of the skin. Melanocytes arise from the neural crest. During embryonic development, melanoblasts migrate toward the dermis, and then through it to reach the overlying epidermis, where they undergo extensive proliferation and begin the production of melanin. In the next step, melanosomes are transferred from melanocytes to keratinocytes[5]. Furthermore, the configuration of the "ordered three-dimensional cellular arrangement" of the skin, called "epidermal melanin unit," also influences the determination of pigmentation[6].

Many genes encode protein components or regulators of signaling pathways involved in the development, migration, and function of melanocytes and, therefore, in the control of physiological and pathological pigmentation of the skin. A large group of syndromes associated with CALS result from germline mutations in these associated genes[7].

In addition to melanocytes, the neural crest gives rise to several other cell types. As a transient structure present during embryonic development, the neural crest is composed of highly multipotent progenitor cells, characterized by populations of already determined precursors and heterogeneous and multipotent cells[6,8], capable of giving rise to different phenotypes, depending on various growth factors and the microenvironment at the migration sites. Thus, the cephalic neural crest gives rise to most of the craniofacial skeleton (chondrocytes, osteocytes and odontoblasts) and other facial tissues such as nerve ganglia, muscles, connective tissue and pigment cells, while the trunk neural crest cells give rise to neurons and glial cells of the peripheral nervous system, in addition to secretory cells of the endocrine system and skin pigment cells[6,9]. This explains the wide phenotypic variation observed in syndromes associated with CALS.

It is important to highlight that isolated CALS may occur as a common finding (10–36% of healthy people) with no clinical significance when dissociated from other findings[4]. However, the presence of multiple CALS, large segmental CALS, other skin anomalies, facial dysmorphism, and other unusual findings on physical examination may suggest the presence of an associated genetic disorder and should be investigated[2].

The study aimed to provide a comprehensive understanding of the syndromes associated with CALS that exhibit craniofacial abnormalities as part of the clinical phenotype.

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METHODS

A review of the literature was conducted from January to July 2021. The identification of genetic diseases associated with CALS was carried out in the *Online Mendelian Inheritance in Man* (OMIM)[10]. The descriptors used for the search were as follows: "genetic diseases" or "hereditary diseases" and "cafe-au-lait spots" or "hyperpigmentation."

Once the related syndromes were identified, the presence (or not) of associated craniofacial abnormalities was determined from a survey carried out at OMIM, using the specific name of each syndrome and observing the signs/symptoms in the clinical synopsis. Subsequently, the evaluation of the clinical signs associated with each syndrome was extended to other databases, such as PubMed (www.pubmed.com) and Virtual Health Library (www.bvsalud.org).

Literature review, case report, and case series were included in the research. Since these are rare diseases, the date filter was not used.

RESULTS

A total of 60 syndromes associated with the presence of CALS are described[11]. Among them, craniofacial abnormalities can be part of the clinical phenotype in 45 syndromes.

The affected gene and the typical, general, craniofacial, and orodental alterations observed in each syndrome are described in Table 1. The identified syndromes were classified into groups according to the altered signaling pathway and/or the function of the mutated gene.

Among the 45 syndromes identified, 39 different genes were recognized, considering that different syndromes can be linked to the same gene and that some entities have not been related to any gene until nowadays.

DISCUSSION

Neurofibromatosis type 1 (NF1) is the disease with the highest incidence among all syndromes associated with CALS and one in which this association is well recognized and considered a diagnostic hallmark[2]. However, several other genetic syndromes are associated with café au lait spots, with a total of 60 syndromes described in the scientific literature[11].

Most of these diseases that present multiple CALS are part of the developmental diseases known as RASopathies. This group includes genetic syndromes caused by germline mutations in genes encoding components of the Ras/MAPK (mitogen-activated protein kinases) pathway. This regulatory pathway is an essential intracellular signaling cascade that controls many cell functions such as differentiation, survival, and proliferation – functions that are critical for normal development[7].

With regard to syndromes associated with CALS and craniofacial abnormalities, most of them are also included in the group of RASopathies. In this condition, we have NF1[7], Legius syndrome[7,12], Leopard syndrome 1[12], Leopard syndrome 2[12], Leopard syndrome 3, Costello syndrome[7,12], cardio-facio-cutaneous syndrome[7,12], Noonan syndrome, Noonan syndrome-like disorder with loose anagen hair 2[13], and Noonan syndrome 13.

Considering that dysregulation of the underlying Ras/MAPK pathway is common to all RASopathies, the diseases included in this classification exhibit numerous overlapping phenotypic characteristics, such as craniofacial dysmorphism, cardiovascular anomalies, abnormalities in tissues of ectodermal origin, neurocognitive impairment, and increased risk of cancer[12].

However, it is important to consider that each of the RASopathies exhibits a unique phenotype, as it is caused by mutations at different points in the metabolic pathway[12]. In this sense, and considering the importance of the Ras/MAPK pathway in craniofacial development, the characterization of craniofacial and orodental changes in each of the RASopathies can provide valuable information for the diagnosis of a specific syndrome[7].

Another group to be considered corresponds to phakomatoses. Defects at any stage of neural crest cell development such as migration, proliferation, cell-to-cell interaction, differentiation, or growth are associated with the pathophysiology of neurocutaneous syndrome or phakomatoses[14]. This group includes pathologies with different genetic mechanisms. The encompassing diseases that share CALS and craniofacial abnormalities are Watson syndrome, Peutz-Jeghers syndrome[15], tuberous sclerosis complex[15], Cowden syndrome[16], McCune-Albright syndrome[17], and Johnson neuroectodermal syndrome[18].

As a common feature in the group, all the diseases represent neurocristopathies and, therefore, include abnormalities in the tissues of ectodermal origin, especially the skin, eyes, and central nervous system[15]. Craniofacial alterations can also occur, mainly related to structures originating from the ectodermal embryonic leaflet[17].

Another important signaling pathway involved in the development and function of melanocytes is the KIT signaling pathway. Waardenburg syndrome type 2E, piebaldism, peripheral demyelinating neuropathy-central dysmyelination-Waardenburg syndrome-Hirschsprung disease, and familial progressive hyperpigmentation with or without hypopigmentation are genetic disorders of aberrant melanoblast differentiation and migration during embryogenesis[5]. The binding of the KIT ligand to its receptor KIT triggers

Table 1. Genetic syndromes associated with CALS and craniofacial abnormalities.

RASopathies	*Gene*	*Typical and general features*	*Craniofacial and orodental manifestation*	*Ref.*
Neurofibromatosis type I	*NF1*	*Typical:* multiple CALS; Lisch nodules; neurofibromas; freckling. Increased risk neoplasms. *General:* mild mental retardation, hydrocephalus; renal artery stenosis; skeletal anomalies.	Macrocephaly, hypoplasia mandibular; hypertelorism; dental irregularities, congenitally missing second molars.	OMIM (162200)[2,7]
Legius syndrome	*SPRED1*	*Typical:* multiple CALS (99%), variable dysmorphic features, lipomas, learning disabilities. Not associated with neurofibromas, optic gliomas, Lisch nodules, or tumor predisposition. *General:* freckling; pectus deformities; learning difficulties, attention deficit-hyperactivity.	Macrocephaly, triangular face, low-set ears; downslanting palpebral fissures, epicanthal folds, hypertelorism; low-posterior hairline; short neck; high arched palate; micrognathia; deeply philtrum.	OMIM (611431)[2,22,23]
Leopard syndrome 1	*PTPN11*	*Typical:* multiple lentigines, hypertelorism, pulmonic stenosis, abnormal genitalia, short stature, electrocardiographic abnormalities, deafness. *General:* CALS (70–80%); mental retardation; thoracic deformities, spina bifida.	Prognathism, triangular face, biparietal bossing; prominent and low-set ears; ptosis, epicanthus folds, strabismus; broad nose; short neck. Cleft palate, deep nasal-labial folds, thick lips, dental anomalies.	OMIM (151100)[7]
Leopard syndrome 2	*RAF1*	*Typical:* short stature, hypertrophic cardiomyopathy, craniofacial anomalies, CALS, lentigines. *General:* delayed puberty; cubitus valgus.	Dolichocephaly; prominent chin; short webbed neck; low-set ears; hypertelorism, downslanting palpebral fissures. Thick lips.	OMIM (611554)
Leopard syndrome 3	*BRAF*	*Typical:* pigmented lesions, short stature, hyperkeratosis, craniofacial anomalies. *General:* lentigines, CALS, multiple nevi spread on the whole body; cognitive deficits, seizures; heart and thoracic defects; delayed bone age.	Low-set ears, sensorineural deafness; short webbed neck; hypertelorism; depressed nasal bridge; curly hair.	OMIM (613707)
Costello syndrome	*HRAS*	*Typical:* coarse facies, short stature, distinctive hand posture, severe feeding difficulty. Predisposition to cancer. Mental retardation. *General:* deep creases, cutis laxa, acanthosis nigricans, papilloma, palmar nevi, isolated CALS (9-31%), multiple CALS (rare); cardiac defect; small lung; renal failure; nail abnormalities.	Macrocephaly, high forehead, bitemporal narrowing; hypertelorism, strabismus, epicanthal folds, ptosis; short nose; full cheeks; low-set ears; short neck. Arched palate, micrognathia, gingival hypertrophy, enamel defect, delayed tooth eruption; thick lips, large mouth, bifid uvula; macroglossia.	OMIM (218040)[7,24,25]
Cardio-facio-cutaneous syndrome syndrome 1	*BRAF*	*Typical:* coarse facies, heart defects, mental retardation. Ectodermal abnormalities, short stature. *General:* one or two CALS (9–31%); multiple CALS (rare), hyperkeratosis, ichthyosis, hemangioma; cortical atrophy, peripheral axonal neuropathy.	Relative macrocephaly, high forehead, bitemporal narrowing, hypertelorism, ptosis, strabismus, epicanthal folds; short nose, low-set ears; webbed neck. Sparse/curly hair. High arched palate, open bite.	OMIM (115150)[7,24,25]
Noonan Syndrome	*PPTN11*	*Typical:* short stature, facial dysmorphism, congenital heart defects. *General:* CALS (frequent), linfedema, skeletal defects, mental retardation, cryptorchidism, bleeding diathesis.	Broad forehead; hypertelorism, downslanting palpebral fissures; low set ears, hearing loss; webbed neck; deeply grooved philtrum, high-arched palate, dental malocclusion.	OMIM (163950)[7,25]
Noonan syndrome 13	*MAPK1*	*Typical:* global developmental delay, behavioral problems, craniofacial anomalies. *General:* lentigines, CALS; cubitus valgus, broad thorax; heart defects. Short stature.	High/broad forehead; long philtrum; low-set ears; ptosis, hypertelorism; wide nasal bridge; short neck; hypertrichosis. Marked upper lip vermilion, everted lower lip; dental anomalies.	OMIM (619087)
Noonan Syndrome-like disorder with loose anagen hair 2	*PPP1CB*	*Typical:* distinctive features of hair and skin, short stature, heart defects. *General:* hypopigmentation, freckling, CALS, loose skin; developmental delay, Chiari I (1 patient), Dandy-Walker malformation (1 patient); delayed bone age; pectus excavatum.	Macrocephaly, prominent forehead, low posterior hairline; large and low-set ears, preauricular pits; hypertelorism, ptosis, epicanthal folds; short and webbed neck. High-arched palate, dental malocclusion.	OMIM (617506)[25]

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Table 1. Continuation.

Neurocutaneous syndrome or phakomatoses	*Gene*	*Typical and general features*	*Craniofacial and orodental manifestation*	*Ref.*
Watson syndrome	*NF1*	*Typical:* pulmonary valvular stenosis, CALS, decreased intellectual ability, short stature. *General:* multiple CALS, neurofibromas, freckling.	Relative macrocephaly, Lisch nodules.	OMIM (193520)
Peutz-Jeghers syndrome	*STK11*	*Typical:* hyperpigmented spots, multiple gastrointestinal hamartomatous polyps, neoplasms. *General:* multiple CALS (unusual); polyps; digital clubbing; precocious puberty.	Hyperpigmented patches (lips and buccal mucosa). Vermilion zone of the lips. Nasal polyps.	OMIM (175200)[26]
Tuberous sclerosis 1	*TSC1*	*Typical:* hamartomas in multiple organ. *General:* white ash leaf-shaped macules, subcutaneous nodules, CALS (<50%), subungual fibromata; epilepsy, mental handicap, paraventricular calcifications; skeletal disorders.	Angiofibromas, fibrous plaques (forehead/ scalp), enamel pits, confluent gingival nodules (cobblestone appearance). Ophthalmic tumors.	OMIM (191100)[23,27]
Tuberous sclerosis 2	*TSC2*	*Typical:* hamartomas in multiple organs. *General:* Same features as tuberous sclerosis 1, with more severe disease.	Angiofibromas, fibrous plaques (forehead/ scalp), enamel pits, confluent gingival nodules (cobblestone appearance).	OMIM (613254)[23,27]
Cowden syndrome 1	*PTEN*	*Typical:* hamartomatous disorder characterized by macrocephaly, acral keratoses, facial trichilemmomas, papillomatous papules, risk for breast, thyroid and endometrial carcinoma. *General:* pigmentation of the glans penis, CALS (<50%), multiple skin tags; mental retardation; vascular anomalies; pectus excavatum; intestinal polyps, colonic diverticulosis.	Macrocephaly; hearing loss; hypoplastic mandible/ maxilla; cataract. Oral papillomas, scrotal tongue, high arched palate, microstomia, gingival hypertrophy, multiple gingival hyperplastic papules.	OMIM (158350)[23,28]
Johnson neuroectodermal syndrome	Not identified	*Typical:* deafness, anosmia, hypogonadotropic hypogonadism, alopecia. Growth retardation. *General:* hypohidrosis, truncal CALS (rare); mental retardation; short stature; heart defect.	Microcephaly (rare); sparse hair; microtia, conductive deafness; absent eyebrows/eyelashes; choanal stenosis. Facial nerve palsy, cleft palate (rare), retrognathia.	OMIM (147770)[29]
McCune-Albright syndrome	*GNAS*	*Typical:* polyostotic fibrous dysplasia, CALM>50% (large and segmental), precocious puberty. *General:* gastrointestinal polyps; pathologic fracture; hyperthyroidism, hyperparathyroidism, acromegaly, hyperprolactinemia, Cushing syndrome.	Craniofacial hyperostosis, facial asymmetry, deafness, blindness; pituitary adenoma.	OMIM (174800) Ref.[23,30]
DNA repair disorders	***Gene***	***Typical and general features***	***Craniofacial and orodental manifestation***	***Ref.***
Bloom syndrome	*WRN/ RECQL3*	*Typical:* pre and postnatal growth deficiency, short stature; facial telangiectatic, hypo/hyperpigmented skin, sun-sensitive; predisposition to malignancy. *General:* CALS (>50%), hypertrichosis, photosensitivity; infertility; digital defects; chronic lung disease; mild mental retardation; recurrent infections.	Dolichocephaly skull, microcephaly, narrow face, prominent ears/nose. Absent upper lateral incisors, highly arched palate.	OMIM (210900)[23]
Nijmegen breakage syndrome	*NBN*	*Typical:* microcephaly, cancer predisposition, short stature, immunodeficiency. *General:* CALS (<50%), vitiligo; mental retardation, hyperactivity, neurodegeneration; primary ovarian failure; radiation hypersensitivity. Premature death.	Typical facial appearance, prominent midface, microcephaly; upward slanting of palpebral fissures; dysplastic ears; choanal atresia, long nose. Periodontal diseases; cleft lip/palate.	OMIM (251260)[23]
Seckel syndrome 2	*RBBP8*	*Typical:* "bird-headed" facial appearance, mental retardation, short stature, microcephaly. *General:* CALS (some); ectopic kidneys; digital defects, slender extremities.	Microcephaly, proptosis; beaklike nose; narrow face, receding mandible; nystagmus; ear defect. Dental anomalies, cleft palate, high arched palate, hypoplastic enamel, macroglossia, gingival hyperplasia.	OMIM (606744)[31]
Nijmegen breakage syndrome-like disorder	RAD50	*Typical:* severe growth restriction; congenital microcephaly, impaired intellectual development. *General:* CALS, multiple nevi; short stature; spasticity, Chiari malformation; brachydactyly, clinodactyly; vascular anomalies, Wolff-Parkinson-White anomaly; widely spaced nipples.	Microcephaly, sloping forehead, micrognathia; hypertelorism; broad nasal bridge; hypoplastic nasal septum.	OMIM (613078)
Fanconi anemia (FANCA, FANCC, FANCI, FANCD2)	*FANCA FANCC FANCI FANCD2*	*Typical:* developmental abnormalities in major organ systems, early-onset bone marrow failure, high predisposition to cancer (leukemia). Small stature. *General:* malformations: skeleton (radial aplasia, thumb deformity, vertebrae defects), skin (CALS, others), cardiopulmonary, gastrointestinal, central nervous systems, urogenital.	Microcephaly; strabismus, microphthalmia. "Fanconi facies"; ear malformations; short neck.	OMIM (227650, 227645, 227646, 609053)

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Table 1. Continuation.

KIT signaling pathway	*Gene*	*Typical and general features*	*Craniofacial and orodental manifestation*	*Ref.*
Waardenburg syndrome type 2E	*SOX10*	*Typical:* auditory-pigmentary syndrome. Congenital hearing loss, neurologic abnormalities. *General:* hypopigmented patches, CALS (mild), premature graying; pectus excavatum.	Ocular albinism, white forelock/ eyelashes/eyebrows; nystagmus; anosmia. Delayed deciduous tooth eruption, large central incisors, irregularly placed dentition.	OMIM (611584)
Familial progressive hyper- and hypopigmentation	*KITLG*	*Typical:* larger hypopigmented ash-leaf macules, diffuse hyperpigmentation, CALS. *General:* lentigines, vitiligo, multiple CALS, hyperkeratosis.	Hyperpigmented patches.	OMIM (145250)
Genomic imprinting disorders	***Gene***	***Typical and general features***	***Craniofacial and orodental manifestation***	***Ref.***
Silver-Russell syndrome 1	*ICR1*	*Typical:* growth retardation, craniofacial features, body asymmetry, others malformations. *General:* CALS (<50%); developmental delay; cardiac defects; digital defects; neoplasms.	Relative macrocephaly, triangular face, prominent forehead; blue sclera; micrognathia, thin lips, downturned corners of mouth, retrognathia.	OMIM (180860)[23]
Mulchandani-Bhoj-Conlin syndrome	*GRCh38*	*Typical:* short stature, profound feeding difficulties. *General:* CALS (infrequent); hypotonia; horseshoe kidney; digital defects.	Microcephaly, triangular face, dolichocephaly, low-set ears, thick helices; epicanthal folds. Retrognathia, narrow palate.	OMIM (617352)
Miscellaneous	***Gene***	***Typical and general features***	***Craniofacial and orodental manifestation***	***Ref.***
Multiple endocrine neoplasia type I	*MEN1*	*Typical:* endocrine tumors. *General:* CALS (40%), hypopigmented macules, lipomas, collagenomas; prolactinoma; vasointestinal peptide tumor, gastrinoma; carcinoid tumors.	Multiple facial angiofibromas, collagenomas. Multiple gingival papules.	OMIM (131100)[23]
Multiple endocrine neoplasia type IIB	*RET*	*Typical:* hamartoneoplastic syndrome: thyroid carcinoma, pheochromocytoma, mucosal neuromas, thick corneal nerves. Failure to thrive. *General:* CALS (sometimes); ganglioneuroma, developmental delay; parathyroid hyperplasia; goiter; colonic diverticulum, megacolon; myopathy, skeletal abnormalities.	Characteristic facial appearance: swollen lips, flat nasal bridge; ptosis. High arched palate, prognathism, thick lips.	OMIM (162300)
Smith-Kingsmore syndrome	*MTOR*	*Typical:* macrocephaly, seizures, umbilical hernia, facial dysmorphic features. *General:* CALS (11.1%); intellectual disability, heterotopic gray matter, corpus callosum hypogenesis, polymicrogyria, hypotonia; small thorax; limb shortening; small toenails.	Midface hypoplasia, frontal bossing; hypertelorism, downslanting palpebral fissures; short nose; curly hair. Macrostomia, long philtrum, thin lip.	OMIM (616638)[32]
Rubinstein-Taybi syndrome 1	*CREBBP*	*Typical:* microcephaly, mental retardation, growth deficiency, broad thumbs/ halluces, dysmorphic facial features. *General:* single transverse palmar creases, CALS; agenesis corpus callosum, seizures; heart defect; sternal anomalies; digital defects; hirsutism.	Striking facial features, low anterior hairline, prominent forehead; strabismus, ptosis; hypoplastic maxilla, micro/retrognathia; low-set ears, hearing loss; beaked nose. Dental anomalies, high-arched palate, malocclusion, hypoplastic enamel, thick lip.	OMIM (180849)
OHDO syndrome, X-linked	*MED12*	*Typical:* blepharophimosis, ptosis; long filter; micrognathia, deafness. *General:* CALS; developmental delay; cryptorchidism; clinodactyly.	Facial coarsening, epicanthal folds; small ears; wide nasal bridge; blepharophimosis, ptosis; microstomia, dental anomalies.	OMIM (300895)
Chung-Jansen syndrome	*PHIP*	*Typical:* impaired global and intellectual development, dysmorphic features, obesity. *General:* CALS (40%); hands: tapering fingers, clinodactyly; feet: syndactyly; hypotonia.	High forehead; large ears; thick eyebrows, hypertelorism, synophrys, epicanthal folds, strabismus. Micrognathia, thin lips, high palate.	OMIM (617991)
Kabuki syndrome	*KMT2D*	*Typical:* mental retardation, postnatal dwarfism, peculiar facies, characteristic skeletal and dermatoglyphic changes. *General:* CALS, cutis aplasia; seizures, hypotonia; heart defect; anal defects; renal anomalies; vertebral/hip anomalies, digital defects.	Microcephaly; long palpebral fissure, eversion of eyelids, arched eyebrows, long eyelashes, hypertelorism; prominent earlobes, hearing loss; wide nose. High palate, cleft lip/palate, bifid tongue/uvula, micrognathia, diastema, dental anomalies.	OMIM (147920)

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Table 1. Continuation.

Miscellaneous	*Gene*	*Typical and general features*	*Craniofacial and orodental manifestation*	*Ref.*
Roberts syndrome	*ESCO2*	*Typical:* tetraphocomelia, mental retardation, cranial/cardiac/renal anomalies. *General:* hypopigmented patches, CALS; rudimentary gallbladder; talipes equine-valgus, rudimentary digits; encephalocele, hydrocephalus. Growth retardation. Short neck.	Microcephaly, craniosynostosis, midfacial hemangioma; exophthalmos, corneal clouding, blue sclera, hypertelorism; hypoplastic nasal alae; malformed ears; fissured lips, high arched palate, cleft lip/palate.	OMIM (268300)
Adams-Oliver syndrome 4	*EOGT*	*Typical:* aplasia cutis and terminal transverse limb defects. *General:* cutis marmorata, CALS (rare); dysplastic/aplastic toenails; temporal/ occipital infarct; heart defect; umbilical hernia; digital defects.	Cutis aplasia and bony defect (scalp).	OMIM (615297)
Johanson-Blizzard Syndrome	*UBR1*	*Typical:* short stature, mental retardation, dysmorphic features. *General:* CALS, scalp defects, tranverse palmar crease; hypotonia; heart defect; small nipples; liver failure; pancreatic insufficiency; imperforate anus; clinodactyly.	Microcephaly; hearing loss; hypertelorism, cutaneous-lacrimal fistulae; hypoplastic nasal wing; blonde and unruly hair. Oligodontia, cleft lip/palate.	OMIM (243800)
Carney complex	*PRKAR1A*	*Typical:* multiple neoplasia syndrome; pigmented lesions. *General:* lentigines, nevi, CALS (<50%); adrenal dysplasia, Cushing disease, acromegaly, thyroid hyperplasia; mammary fibroadenoma, pheochromocytoma, pituitary adenoma.	Conjunctival pigmentation, eyelid myxoma; hirsutism, red hair.	OMIM (160980)[4,23]
Russell-Silver syndrome, X-linked	Unknown	*Typical:* pigmentary anomaly, X-linked – severe in males, mild in females. *General:* CALS; achromatic areas of trunk and limbs; growth retardation.	Triangular facies.	OMIM (312780)
Chromosome 17q11.2 deletion syndrome	Not reported	*Typical:* variable facial dysmorphism, mental retardation, excessive number neurofibromas, increased risk for malignant peripheral nerve tumors. *General:* CALS (93%), freckling; attention-deficit hyperactivity disorder; tall stature; heart defects; pectus excavatum; bone cysts, large hands/feet.	Macrocephaly; coarse facies; Lisch nodules (93%), hypertelorism, optic glioma.	OMIM (613675)
Chromosome 15q26-qter deletion syndrome	*IGF1R*	*Typical:* deletion of chromosome 15q26-qter encompassing the insulin-like growth factor 1 receptor gene. Short stature is stablished hallmark. *General:* CALS; mental retardation; congenital cardiac anomalies; digital defects.	Microcephaly; low-set ears; blepharophimosis, strabismus; broad bridge nose.	OMIM (612626)
Microcephaly, growth restriction and increased sister chromatid exchange 2	*TOP3A*	*Typical:* growth restriction with short stature, microcephaly. *General:* CALS; mild developmental delayed; dilated cardiomyopathy.	Microcephaly; dysmorphic facial features progeroid-like.	OMIM (618097)
Autosomal recessive primary microcephaly	*CDK5RAP2*	*Typical:* microcephaly, developmental delay, variable dysmorphic facies. *General:* CALS; behavioral problems; atrophic cortical, absence of corpus callosum, seizures.	Microcephaly; conical-shaped and widely spaced teeth; hearing loss; prominent nose.	OMIM (604804)
Ring chromosome 14 syndrome	*RC14R MAX*	*Typical:* developmental delay, early-onset epilepsy, microcephaly, dysmorphic facial features. *General:* Pigmentary abnormalities, CALS; hypotonia, seizures, poor speech. Short stature.	Micro/dolichocephaly; low-set ears; downslanting palpebral fissures, epicanthal folds, hypertelorism; flat nasal bridge, anteverted nostrils.	OMIM (616606)[2]
Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	*CBL*	*Typical:* facial dysmorphism, cardiac disease, reduced growth, cognitive deficits, ectodermal/ musculoskeletal anomalies. Susceptibility to juvenile myelomonocytic leukemia. *General:* CALS, lymphedema, thin skin; delayed psychomotor development; language delay; cubitus valgus, joint laxity; pectus excavatum, widely spaced nipples.	Thin hair; frontal bossing, triangular face, long philtrum; large ears, low-set ears; hypertelorism, ptosis, downslanting palpebral fissures; depressed nasal bridge, thick lips.	OMIM (613563)
Microcephalic osteodysplastic primordial dwarfism type II	*PCNT*	*Typical:* severe short stature, microcephaly. Skeletal malformations. *General:* CALS, hypopigmentation; mental retardation, aneurysms; digital defects.	Retrognathia; small ears; prominent nasal root. Enamel hypoplasia, microdontia.	OMIM (210720)

CALS: cafe-au-lait spots; OMIM: Online Mendelian Inheritance in Man; Ref.: reference.

the Ras/MAPK signaling pathway, which regulates the differentiation, migration, and survival of melanocytes, as well as proliferation, melanogenesis, and melanosome transfer[7]. Among the diseases of this group, Waardenburg syndrome and familial progressive hyper- and hypopigmentation are those that present associated craniofacial alterations.

Bloom syndrome, Nijmegen breakage syndrome, Seckel syndrome 2, and Fanconi anemia are diseases that present CALS and craniofacial alterations classified as DNA repair disorders. Germline pathogenic mutations in genes encoding key proteins in DNA repair and telomeres biology result in a high risk of cancer associated with these syndromes[18,19].

In addition, we have the genomic imprinting disorders, associated with an epigenetic phenomenon that causes genes to be expressed or not, inherited from the mother or father. Silver-Russell syndrome 1[20] and Mulchandani-Bhoi-Conlin syndrome[21] are diseases of this group.

Besides these classifications, localized or generalized melanotic hyperpigmentation might be part of the clinical presentation of many other congenital systemic disorders that result from ubiquitous protein defects and/or basal cell processes. This suggests that melanocytes are a cell type with high sensitivity to such perturbations[6]. In these cases, CALS occurs as isolated lesions with low occurrence.

CONCLUSION

The observation of CALS in the assessment of a patient can be of great significance, especially the presence of multiple CALS, large and segmental CALS, other skin anomalies, facial dysmorphism and orodental changes, and other unusual findings on physical examination. These findings should suggest an associated genetic disorder.

Furthermore, it is important to highlight that the craniofacial structures and skin tissue share a similar embryological origin. Thus, the characterization of craniofacial abnormalities in the assessment of a patient with a genetic syndrome associated with CALS can be of great relevance for the diagnosis of the specific syndrome related to this condition.

AUTHORS' CONTRIBUTIONS

AAC: Conceptualization, Research, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review and editing. **DRBM:** Formal analysis, Writing – review and editing. **LDAF:** Research, Data Curation, Formal Analysis, Writing – Original Draft, Writing – review and Editing. **RAM:** Data curation, Formal analysis, Writing – original draft, Writing – review and editing. **HMJ:** Conceptualization, Data curation, Formal analysis, Project administration, Writing – review and editing.

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