Cafe-au-lait spots as a clinical sign of syndromes
Manchas café-com-leite como um sinal clínico de síndromes
Manchas café con leche como signo clínico de síndromes

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Abstract
Several studies describe the frequent association of cafe-au-lait spots with neurofibromatosis. However, many other genetic diseases might be associated with the presence of café-au-lait spots. Several genetic diseases are rare. In most cases, syndromes present themselves as a set of signs and symptoms that may present varied penetrance, therefore largely reducing the percentage of final diagnosis. Exploration of clinical symptomatology is essential for the understanding and diagnosis of syndromes. In this review, we conduct an extensive literature search looking for research that investigated diseases that may be present simultaneously with the cafe-au-lait spots. A total of 60 genetic diseases were found, all of them rare. These syndromes were evaluated based on their most relevant features and described in a summary of the typical, general, and head and neck findings. The available OMIM number, mode of inheritance, chromosome, mutated genes, and affected proteins were also listed. The considerable variety of diseases associated with the presence of cafe-au-lait spots and the fact that many of these conditions affect various organ systems with diverse phenotypic presentations is a diagnostic and therapeutic challenge. The objective of this study was to provide health professionals with an instrument containing a broad spectrum of genetic diseases coincident with the presence of cafe-au-lait spots in order to facilitate the differential and final diagnosis of these syndromes.

Keywords: Cafe-au-lait spots; Hyperpigmentation; Neurofibromatosis; Inborn genetic diseases; Hereditary syndromes.

Resumo
Vários estudos descrevem a associação frequente de manchas café-com-leite com neurofibromatose. No entanto, muitas outras doenças genéticas podem estar associadas à presença de manchas café-com-leite. Várias doenças genéticas são raras. Na maioria dos casos, as síndromes se apresentam como um conjunto de sinais e sintomas que podem apresentar penetrância variada, reduzindo bastante o percentual de diagnóstico final. A exploração da sintomatologia clínica é essencial para a compreensão e diagnóstico das síndromes. Nesta revisão, realizamos uma extensa investigação bibliográfica em busca de pesquisas que avaliaram doenças que podem estar presentes simultaneamente com as manchas café-com-leite. Um total de 60 doenças genéticas foram encontradas, todas raras. Essas síndromes foram avaliadas com base em suas características mais relevantes e descritas em um sumário contendo os achados típicos, gerais e da cabeça e pescoço. O número OMIM disponível, modo de herança, cromossomo, genes mutados e proteínas afetadas também foram listados. A considerável variedade de doenças associadas à presença de manchas café-com-leite e o fato de que muitas dessas condições afetam vários sistemas orgânicos com diversas apresentações fenotípicas é um desafio diagnóstico e terapêutico. O objetivo deste estudo foi fornecer aos profissionais de saúde um instrumento contendo um amplo espectro de doenças genéticas associadas à presença de manchas café-com-leite, a fim de facilitar o diagnóstico diferencial e final dessas síndromes.
Cafe-au-lait spots (CALS) or cafe-au-lait macules (CALM) are characteristically well-defined lesions, with a homogeneous light brown or medium to dark brown spots in dark-skinned people, that might be found all over the body except for the scalp, palms and soles (Hamm, Emmerich & Olk, 2019). Morphologically, they have been described as oval-shaped and with smooth edges or irregular contours, ranging in size from 0.2 cm to 30 cm in diameter, being smaller in young children since they increase proportionally to the body surface (Fistarol & Itin, 2010; Shah, 2010; Hamm et al., 2019). Histologically, they present increased melanin content in both melanocytes and basal keratinocytes, with giant melanosomes also being observed (Shah, 2010). They should be distinguished from lentigo (small pigmented spots with clearly defined edges, varying in size from 2 to 20 mm, usually smaller than 1 cm, that might occur anywhere on the skin) and nevus (a congenital or acquired usually highly pigmented area on the skin, flat or raised), clinical entities that alone will not be analyzed in this study (Fistarol & Itin, 2010).

CALM may be present at birth or develop in the first years of life, which occurs in most cases (Hamm et al, 2019). Isolated CALM is a common finding (10-36% of healthy people) with no clinical significance when dissociated from other findings (Rivers et al., 1985; Hamm et al, 2019). However, the presence of multiple CALMs, large segmental CALM, other cutaneous anomalies, associated facial dysmorphism or unusual findings on physical examination, may suggest the possibility of an associated genetic disease and should be promptly investigated (Shah, 2010).

Several steps are involved in determining skin color, such as lineage specification from embryonic neural crest cells (melanoblasts), melanoblast migration to skin of the embryo; proliferation and survival of the melanocytes in the basal layer of the epidermis; biogenesis of the melanosomes in the melanocytes; production of melanin granules in the melanosomes; translocation of melanosomes from the perinuclear region to the peripheral region of the melanocytes; transfer of the melanosomes from the melanocytes to the keratinocytes; and translocation of the transferred melanin granules from the peripheral region to the supranuclear region of the keratinocytes (Cichorek, Wachulska, Stasiewicz & Tymińska, 2013; Oiso, Fukai, Kawada & Suzuki, 2013). In parallel, a complex melanogenic paracrine network between the mesenchymal and epithelial cells regulates the processes involved in determining skin color after birth (Picardo & Cardinali, 2011; Oiso et al., 2013).

Multiple genes encode component proteins or signaling pathway regulators that control these paracrine network and the melanogenic growth factors which play a crucial role in the control of physiological and pathological skin pigmentation (Picardo...
In this category are the KITLG gene, which encodes the Kit ligand (ligand for the receptor-type protein-tyrosine kinase KIT) and the proto-oncogene c-KIT encoding the receptor tyrosine-protein kinase KIT, which activate the Ras/mitogen-activated protein kinase (RAS/MAPK) signaling pathway (Picardo & Cardinali, 2011; Oiso et al., 2013; Zhang, Li & Yao, 2016). Kit signaling plays an important role in a variety of physiological processes that occur in many cell types in the body, such as hematopoietic stem cells, mast cells, melanocytes, and germ cells (Ronnstrand, 2004). The RAS family comprises genes expressed in several types of normal cells: H-RAS, N-RAS, and K-RAS, which plays an important role in intracellular signaling pathways and in the regulation of functions such as cell cycle control, differentiation, growth, and cell senescence (Boquett & Ferreira, 2010). A large group of diseases associated with CALM result from germline mutations in these associated genes.

This article provides a critical review of the literature on genetic syndromes associated with CALM. In addition, the genotypic and phenotypic alterations of the identified diseases are described.

2. Methodology

We conducted a bibliographical research from September 2020 to January 2021, looking for studies that investigated diseases that can present CALM as a clinical manifestation. The compendium of human genes and genetic diseases OMIM (Online Mendelian Inheritance in Man) was used as the main source of data for the identification of associated syndromes. The descriptors used for research were: “cafe-au-lait spots”, “hyperpigmentation”, “neurofibromatosis”, “inborn genetic diseases” and “hereditary syndromes”.

Through a critical analysis of the literature, this narrative review was designed to provide a comprehensive understanding of the syndromes associated with CALM, in order to contribute to health professionals, facilitating the differential and final diagnosis of these syndromes. These objectives are in alignment with the reported by Oates & Harris (2015) on the importance of this scientific methodology, either to inform practice and to provide a comprehensive understanding of what is known about a topic.

The genotypic and phenotypic manifestations, as well as the dysmorphic changes in the head and neck of the identified syndromes, were obtained from the OMIM and Orphanet (Online database of rare diseases and orphan drugs) databases, and the book Gorlin's Syndromes of the Head and Neck (Hennekam, Allanson, Krantz, & Gorlin, 2010). Then, the search was expanded to other databases, such as PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Virtual Health Library (VHL) (www.bvsalud.org). No limits were established regarding the date of the published works.

3. Results

Several genetic syndromes can be associated with CALM, all of them rare in occurrence. In the research conducted at OMIM, a total of 60 associated genetic diseases were identified. These syndromes were classified into subsections based on their most relevant features and described in a summary of typical, general, and head and neck findings (Table 1). Among the 60 diseases identified, 40 of them had frequent and significant changes in pigmentation or skin formation. Multiple CALMs are part of the clinical manifestation of at least 29 of these syndromes. In most other syndromes, the presence of CALM was simply an occasional finding, with a total number of affected patients too small to establish any overall rate of involvement, or its presence is not relevant compared to other more evident clinical characteristics.
Table 1. Genetic syndromes reported with cafe-au-lait spots: features (classified according to the most relevant changes).

| Highlighted changes: skin | Others features | Ref. |
|--------------------------|-----------------|------|
| Neurofibromatosis type I | Typical: multiple CALMs; Lisch nodules; cutaneous/sabcutaneous/plexiform neurofibromas; axillary and inguinal freckling. | OMIM (162200) |
| General: mental retardation (mild), hydrocephalus, learning disabilities; renal artery stenosis, hypertension; spina bifida; scoliosis, pseudoarthrosis, local bone overgrowth; hypothalamic tumor, neurofibrosarcoma, rhabdomyosarcoma, duodenal carcinoid, somatostatinoma, phaeochromocytoma, astrocytoma, menigioma, parathyroid adenoma, malignant peripheral nerve and central nervous system tumors. | |
| H&N: macrocephaly, splenoid dysplasia; hypertelorism, choroidal spots, optic glioma. | OMIM (101000) |
| Neurofibromatosis type II | Typical: multiple neoplasia syndrome: tumors in the eighth cranial nerve (90%), meningiomas, schwannomas. | |
| General: CALM (40%), neurofibroma; ataxia, peripheral neuropathy; glioma, ependymoma, astrocytoma, vestibular schwannoma. | |
| H&N: hearing loss; lenticular opacities, retinal hamartoma. | |

| Highlighted changes: skin | Others features | Ref. |
|--------------------------|-----------------|------|
| Legius syndrome | Typical: multiple CALMs, variable dysmorphic features, lipomas, mild learning disabilities. | OMIM (61431) |
| General: freckling; deficit attention; pectus deformities; hypotonia. | |
| H&N: macrocephaly; triangular face; short neck, low-set ears; hypertelorism, downsizing palpebral fissures, epicantal folds, ptosis; micrognathia; low-posterior hairline. | |
| Multiple cafe-au-lait spots | Typical: multiple CALMs without other neurofibromatosis changes. | OMIM (114030) |
| General: CALMs. | Madson, 2012 |
| H&N: no specific changes. | |
| McCune-Albright syndrome | Typical: polystotic fibrous dysplasia, CALM, precocious puberty. | OMIM (174800) |
| General: gastrointestinal polyps; pathologic fracture; hyperthyroidism, hyperparathyroidism, Cushing syndrome, hyperprolactinemia, acromegaly. | Hamm, 2019 |
| H&N: craniofacial hyperostosis, facial asymmetry, deafness, blindness; pituitary adenoma. | |
| Gastrocutaneous syndrome | Typical: peptic ulcer, hiatal hernia and multiple lentigines/CALMs. | OMIM (137270) |
| General: multiple lentigines/CALMs. | Hamm,2019 |
| H&N: hypertelorism, myopia. | Halal,1982 |
| Familial progressive hyperpigmentation | Typical: patches of hyperpigmentation in the skin. | OMIM (614233) |
| General: hyperpigmentation – present as diffuse hyperpigmentation, or as dots, streaks, patches, whorls; CALM. | |
| H&N: no specific changes. | |
| Familial progressive hyperpigmentation and hypopigmentation | Typical: diffuse hyperpigmentation and larger hypopigmented ash-leaf macules. | OMIM (145250) |
| General: progressive hyperpigmentation (trunk, limbs, palms, soles) and hypopigmentation, multiple CALMs, lentigines, vitiligo (rare); hyperkeratosis. | Zeng, 2016 |
| H&N: hyperpigmented patches (face, neck, oral mucosa). | Amyere, 2011 |
| Adams-Pla syndrome | Typical: aplasia cutis and terminal transverse limb defects. | OMIM (615297) |
| General: cutis marmorata, CALM (rare); dysplastic/aplastic toenails; temporal/occipital infarct; heart defect; umbilical hernia; digital defects. | |
| H&N: cutis aplasia and bony defect (scalp). | |
| Piebald trait (piebaldism) | Typical: depigmented patches: skin and hair; CALM and freckling - not usual features. | OMIM (172800) |
| General: white forelock; absent pigmentation: forehead, eyebrows, chin, chest, abdomen, limbs; Hirschspring disease; frequent epiphelomas. | Hamm, 2019 |
| H&N: occasional deafness; heterochromia iridis. | Osro, 2013 |
| Cowden syndrome 1 | Typical: macrocephaly, acral keratoses, facial trichilemmomas, papillomatous papules, increased risk for carcinoma. | OMIM (158350) |
| General: CALM-penis, body; multiple skin tags; multiple hamartomas; vascular anomalies; pectus excavatum; vaginal/vulvar/ovarian cysts; gynecomastia; gastrointestinal polyps, colonic diverticulosis; seizure, Lhermitte-Duclos disease, mental retardation (12%); meningioma, neureomas. | Hamm, 2019 |
| H&N: 'Birdlike' facies; hearing loss; cataract, angiod streak; microstomia, oral papillomas, scrotal tongue. | Guimarães,2002 |
| Peutz-Jeghers syndrome | Typical: melanocytic macules: lips, buccal mucosa, digits; multiple gastrointestinal polyps; increased risk of neoplasms. | OMIM (175200) |
| General: hyperpigmented spots: CALM (unusual); bronchial polyps; biliary tract polyps; hamartomatous polyps (stomach to rectum); ovarian cysts; uralteral polyps, bladder polyps; clubbing of fingers; precocious puberty; gastrointestinal carcinoma, breast cancer, thyroid cancer, lung/pancreatic/uterine/ovarian cancers. | Platara, 2018 |
| H&N: 'Birdlike' facies; hearing loss; cataract, angiod streak; microstomia, oral papillomas, scrotal tongue. | |
| Carney complex | Typical: multiple neoplasia syndrome: cardiac, endocrine, cutaneous, neural myxomatous tumors; pigmented lesions of the skin and mucosa. | OMIM (160980) |
| General: lentigines; blue nevi/other nevi; CALM; schwannoma; pigmented adrenal dysplasia, Cushing disease, acromegaly, thyroid hyperplasia; adrenocortical hyperplasia, Sertoli cell tumor, pituitary adenoma, mammary fibroadenoma, thyroid carcinoma, phaeochromocytoma; atrial/ventricular myxoma. | Hamm, 2019 |
| Condition                                                                 | Features                                                                                           | Ref.                      |
|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------|
| **Leopard syndrome 1**                                                    | Typical: multiple lentigines, electrocardiographic abnormalities, hypertelorism, pulmonic stenosis, abnormal genitalia, short stature, sensorineural deafness. **General:** CALM (50%); mental retardations (mild); heart defects; thoracic deformities; small penis; hypoplastic ovarian; renal agenesis; spina bifida, delayed puberty. **H&N:** prognathism, triangular face, short nose; low-set ears; ptosis, epicanthal folds, strabismus; broad nose; cleft palate. | OMIM (151100) Sarkozy, 2008 |
| **Leopard syndrome 2**                                                    | **Typical:** short stature, hypertrophic cardiomyopathy, craniofacial anomalies, lentigines, CALM. **General:** cardiac changes; delayed puberty. **H&N:** dolichocephaly, prominent chin, short neck; low-set ears; downsizing palpebral fissures, hypertelorism. | OMIM (615554)             |
| **Leopard syndrome 3**                                                    | **Typical:** pigmented lesions, hypertelorasis, short stature, craniofacial anomalies. **General:** lentigines, CALM, multiple nevi; cognitive deficits (mild); heart and thoracic defects; delayed bone age. **H&N:** low-set ears, hearing loss; hypertelorism; depressed nasal bridge; short/webbed neck; curly hair. | OMIM (613707)             |
| **Neurofibromatosis-Noonan syndrome**                                    | **Typical:** combines features: neurofibromatosis and Noonan syndrome. **General:** CALM, freckling, neurofibroma; developmental delay; short stature; pulmonic stenosis; sternum defects; optic glioma. **H&N:** macrocephaly; face hypoplasia; low-seater ears; hypertelorism, downsizing palpebral fissures, ptosis, epicanthal folds, Lisch nodules; short neck. | OMIM(601321) Nyström, 2009 Nystrom, 2007 |
| **Watson syndrome**                                                      | **Typical:** pulmonary valvular stenosis, CALM, cognitive deficit, short stature. **General:** multiple CALMs, neurofibromas, freckling. **H&N:** relative macrocephaly, Lisch nodules. | OMIM(193520) Hamn, 2019 Allanson, 1991 |
| **Bloom syndrome**                                                       | **Typical:** short stature; hypo/hyperpigmented skin, facial telangiectatic; predisposition to malignancy. **General:** CALM, hypertonichrosis, photosensitivity; mild mental retardation; chronic lung disease; azospermia; digital defects. **H&N:** dolichocephaly, microcephaly; narrow face; prominent ears and nose; absent upper lateral incisors; high-pitched voice. | OMIM (210900) Rosales-Solis, 2016 Arora, 2014 |
| **Russell-Silver syndrome, X-linked**                                    | **Typical:** pigmentary anomaly, X-linked – severe in males, mild in females. **General:** CALM; achromatic areas of trunk and limbs; prenatal growth retardation. **H&N:** triangular facies. | OMIM (312780)             |
| **Turner syndrome**                                                      | **Typical:** retarded growth, gonadal dysgenesis, infertility. **General:** CALM (association with NF1); ovarian failure; bone anomalies; lymphedema; cardiac/renal anomalies; thyroid and gastrointestinal involvement. **H&N:** round face, micrognathia, webbed neck, low posterior hairline; deafness. | ORPHA (881) Hatisoglu, 2010 |
| **Nijmegen breakage syndrome**                                           | **Typical:** microcephaly, short stature, immunodeficiency, predisposition to cancer (lymphoma, glioma, medulloblastoma, rhabdomyosarcoma). Premature death. **General:** CALM, progressive vitiligo; mental retardation, hyperactivity, neurodegeneration; anal stenosis/ataxia; primary ovarian failure. **H&N:** microcephaly, prominent midface, upward slanting of palpebral fissures; large dysplastic ears; choanal atresia, cleft lip/palate. | OMIM (251260)             |
| **Nijmegen breakage syndrome-Like disorder**                            | **Typical:** severe prenatal growth retardation and persistent postnatal growth restriction, congenital microcephaly, borderline to mildly impaired intellectual development, normal sexual development and radioresistant DNA synthesis with no immunodeficiency, myelodysplasia, or early neurodegeneration. **General:** CALM, multiple pigmented nevi; short stature; developmental delay, spasticity, ataxia, Chiari malformation; brachydactyly, cimodactyly, sandal gap; widely spaced nipples; cutaneous vascular anomalies, Wolff-Parkinson-White anomaly. **H&N:** microcephaly, sloping forehead, micrognathia; hypertelorism; broad nasal bridge; hypoplastic nasal septum. | OMIM(613078)               |
| **Johnson neuroectodermal syndrome**                                     | **Typical:** anosmia and hypogonadotropic hypogonadism, conductive deafness, alopecia, other variable anomalies. **General:** hypohidrosis, multiple trunci CALM (rare); mental retardation; short stature; heart defect; hypogonadism; small penis. **H&N:** alopecia, microcephaly; protruding ear, microtia, external auditory canal atresia; absent eyebrows/eyelashes; choanal stenosis; cleft palate. | OMIM(147770) Hamm, 2019   |
| **Noonan Syndrome-like disorder with loose anagen hair 2**               | **Typical:** distinctive hair anomaly; heart defects; distinctive skin features; short stature. **General:** freckling, CALM, hypopigmentation; loose/thin skin; developmental delay, Chiari I, Dandy-Walker malformation; delayed bone age. **H&N:** macrocephaly, craniosynostosis; preauricular pits, low-set ears; hypertelorism, downsizing palpebral fissures, ptosis; arched palate; short neck; sparse hair. | OMIM (617506)             |
| **Noonan Syndrome-like disorder with or without juvenile myelomonocytic leukemia** | **Typical:** facial dysmorphism, wide spectrum of cardiac disease, reduced growth, variable cognitive deficits, ectodermal and musculoskeletal anomalies. **General:** CALM, lymphedema; thin skin; hypotonia; delayed psychomotor development (mild); language delay; increased susceptibility to juvenile myelomonocytic leukemia; joint laxity, cubitus valgus; cryptorchidism; pectus excavatum, widely spaced nipples; congenital heart defects, aortic stenosis, mitral insufficiency. | OMIM (613563)             |


**Microcephalic osteodysplastic primordial dwarfism type II**

**Typical:** severe short stature, microcephaly.

**General:** CALM, hypopigmentation; mental retardation, multiple aneurysms; narrow chest; digital defects, delayed bone age; short bones; premature puberty.

**H&N:** microcephaly; retrogнатia; small ears; upward-slaingting palpebral fissures; prominent nasal root; enamel hypoplasia, microdontia.

**OMIM:** 210720

Nishimura, 2004

Young, 2004

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**Ataxia-telangiectasia**

**Typical:** cerebellar cortical degeneration and ataxia, telangiectasias, immune defects, predisposition to cancer. Short stature.

**General:** CALM, sceleroderma, pseudocysts; dystrophic, choreothetosis, myoclonus, seizures; lymphoma, leukemia; immunodeficiency; hypogonadism.

**H&N:** ocular telangiectasia, oculomotor abnormalities; progeric changes.

**OMIM:** 208900

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**Noonan syndrome 6**

**Typical:** short stature, facial dysmorhism, heart defects.

**General:** keratosis pilaris, hyperkeratosis, lentigines, CALM; developmental delay; cardiac defects; thorax deformity; juvenile myelomocytic leukemia, polyhydramnios and single umbilical artery.

**H&N:** microcephaly, low-set ears, hearing loss; epicanthal folds, downslanting palpebral fissures; long eyebrows; broad nasal bridge; webbed neck; sparse hair.

**OMIM:** 613224

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**Noonan syndrome 13**

**Typical:** developmental delay and impaired intellectual development, associated with behavioral problems. Reduced postnatal growth and craniofacial anomalies.

**General:** multiple lentigines, CALM, hypocromic spots; hypotonia, seizures, attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety; cubitus valgus, pes planus; hypospadias, cryptorchidism; broad thorax, scapular winging, widely spaced nipples; heart defects prolapse; hypertrichosis; low posterior hairline.

**H&N:** high/broad forehead, long philtrum; low-set ears; ptosis, hypertelorism, epicanthal folds; wide nasal bridge, everted lower lip; dental changes; short neck.

**OMIM:** 619087

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**Johanson-Blizzard syndrome**

**Typical:** short stature, mental retardation, variable dysmorphic features.

**General:** CALM, scalp aplasia cutis, transverse palmar crease; hypoplasia, heart defect; small nipples, absent areolae; liver failure; pancreatic insufficiency; imperforate anus; microopenis; delayed bone age, cildactyly.

**H&N:** microcephaly; hearing loss; strabismus, cutaneous-lacral fistulae; beaked nose; hypoplastic teeth, absent permanent; blonde/unruly hair.

**OMIM:** 243800

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**Roberts syndrome**

**Typical:** tetraphocomelia, growth retardation, mental retardation, craniofacial/cardiac/renal anomalies.

**General:** midfacial capillary hemangiomia, CALM; encephalocele, hydrocephalus; heart defect; rudimentary gallbladder; enlarged penis or clitoris; polycystic kidney; digital defects, talipes equinovarus; mouchi cystic hygroma.

**H&N:** microcephaly, brachycephaly, craniosynostosis; malformed ears; hypertelorism, bluish sclerae; widened nasal bridge; cataract, downslanting palpebral fissures; cleft lip/palate; short neck; silvery blonde sparse hair.

**OMIM:** 268300

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**Cardiofaciocutaneous syndrome 1**

**Typical:** distinctive coarse facies, heart defects, mental retardation. Ectodermal abnormalities. Short stature.

**General:** atopic dermatitis, ichthyosis, hyperkeratosis, cavernous hemangiomia, multiple palmar creases, lentigines, CALM (9-31%); seizures, hypotonia/hiyperorponsia, cortical atrophy, hypoplasia corpus callosum; peripheral axonal neuropathy; delayed bone age, cildactyly.

**H&N:** macro/dolichocephaly; micrognathia; low-set ears, hearing loss; ptosis, nystagmus, strabismus, downslanting palpebral fissures, hyperelorism, epicanthal folds, loss of visual acuity; absence eyebrows/eyelashes; cleft palate, clefts, sparse hair.

**OMIM:** 115150

Hamm, 2019

Zhang, 2016

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**Costello syndrome**

**Typical:** characteristic coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty. Significant cancer risk.

**General:** cutis laxa, redundant skin, deep palmar/plantar creases, CALM (rare), papilloma, acanthosis nigricans, palmar nevi; mental retardation, cerebral atrophy, cerebellar tonsillar herniation; cardiac defect; small lung; renal failure; wide distal phalanges; nail changes.

**H&N:** macrocephaly, micrognathia; low-set ears; hypertelorism, epicanthal folds, downslanting palpebral fissures, ptosis, strabismus; macroglossia; depressed nasal neck; sparse hair; hoarse voice.

**OMIM:** 218040

Zhang, 2016

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**Mismatch repair cancer syndrome (MMRCS1, MMRCS2, MMRCS3, MMRCS4)**

**Typical:** cancer predisposition syndrome with 4 main tumor types: hematologic malignancies, brain tumors, colorectal tumors, multiple intestinal polyps.

**General:** CALM, freckling, neurofibromas, Plexiform neurofibromas; agenesis of the corpus callosum, gray matter heterotopia, intracerebral cysts; colonic polyps; ependymoma, glioblastoma, oligodendroglioma, neuroblastoma, astrocytoma, medulloblastoma, basal cell carcinoma, colorectal adenocarcinoma, leukemia, lymphoma.

**H&N:** no specific changes.

**OMIM:** 276300, 619096, 619097, 619101

Hamm, 2019

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**Tuberous sclerosis 1**

**Typical:** hamartomas in multiple organ systems.

**General:** white ash leaf-shaped macules, subcutaneous nodules, CALM, subungual fibromata; hamartomatous (brain), subependymal nodules, cortical tubers, attention-deficit hyperactivity disorder; seizures, mental retardation, intracranial calcification, autism; Wolf-Parkinson-White; kidney tumors, myocardial rhadomyoma, renal carcinoma, ependymoma, astrocytoma, benign tumors; precocious puberty.

**OMIM:** 191100
| Syndrome/Deletion Syndrome | Others features | Ref. |
|-----------------------------|-----------------|-----|
| Tuberous sclerosis 2 | **H&N:** facial angiofibroma, retinal astrocytoma, optic gliomas; gingival fibroma. **Typical:** hamartomas in multiple organ systems. More severe disease than type-1. **General:** white ash leaf-shaped macules, subcutaneous nodules, CALM, subungual fibromata; hamartomatous (brain), subependymal nodules, cortical tubers, seizures, mental retardation, intracranial calcification, attention-deficit hyperactivity disorder, autism; Wolf-Parkinson-White; kidney tumors, myocordial rhabdomyoma, renal carcinoma, ependymoma, astrocytoma, benign tumors; precocious puberty. **OMIM:** (613254) | Veenma, 2010 |
| Neurofibromatosis, type III | **OMIM:** (162260) | Veenma, 2010 |
| Waardenburg syndrome type 2E | **OMIM:** (611584) | Veenma, 2010 |
| Chromosome 17q11.2 deletion syndrome | **OMIM:** (613675) | Veenma, 2010 |
| Mulchandani-Bhoj-Conlin syndrome | **OMIM:** (617352) Mulchandani, 2016 | Mulchandani, 2016 |
| Silver-Russell syndrome 1 | **OMIM:** (180860) Spiteri, 2017 |
| Chromosome 15q26-pter deletion syndrome | **OMIM:** (612626) Veenma, 2010 |
| Seckel syndrome 2 | **OMIM:** (606744) Veenma, 2010 |
| Rubinstein-Taybi syndrome | **OMIM:** (180849) |
| Kabuki syndrome 1 | **OMIM:** (147920) Ghada, 2011 |
| Microcephaly, growth restriction and increased sister chromatid exchange 2 | **OMIM:** (618097) | ||
| Syndrome/Condition | Typical Signs | General Signs | Ref. |
|--------------------|--------------|--------------|-----|
| **OHDO syndrome, X-linked** | Distinct blepharophimosis-mental retardation syndrome. | CALM; developmental delay; low weight; scrotal hypoplasia; clinodactyly. | OMIM (300895) |
| **Autosomal recessive primary microcephaly** | Microcephaly, developmental delay, variable dysmorphic facies. | CALM; behavioral problems; small cerebral cortex, simplified gyral pattern, partial absence of the corpus callosum, tonic clonic seizures. | OMIM (604804) Pagnamenta, 2012 |
| **Smith-Kingsmore syndrome** | Macrocephaly, seizures, umbilical hernia, facial dysmorphic features. | CALM; intellectual disability, hypogenensis of the corpus callosum, polymicrogyria, heterotopic gray matter, autistic features; small thorax; diastasis recti, umbilical hernia; limb shortening, deep palmar/plantar creases, short phalanges, small toenails; hypotonia. | OMIM (616638) |
| **Developmental delay, intellectual disability, obesity, and dysmorphism** | Developmental delay, intellectual disability, behavioral abnormalities, dysmorphic features, obesity. | CALM; attention deficit-hyperactivity disorder; hands: tapering fingers, clinodactyly; feet: syndactyly; hypotonia. | OMIM (617991) Jansen, 2018 |
| **Ring chromosome 14 syndrome** | Early-onset epilepsy, developmental delay with mental retardation, microcephaly, dysmorphic features. | CALM; short stature (less frequently observed s | OMIM (616606) Rinaldi, 2017 |
| **Genetic susceptibility to neuroblastoma** | Genetic predisposition to neuroblastoma tumors. | CALM; paraneoplastic syndromes, opsoclonus, myoclonus, ataxia, spinal cord compression; neuroblastoma; ganglioneuroma. | OMIM (256700) Origone, 2003 Chatten, 1967 |

**Highlighted changes:**

**endocrine**

| Syndrome/Condition | Typical Signs | General Signs | Ref. |
|--------------------|--------------|--------------|-----|
| **Pheochromocytoma-islet cell tumor syndrome** | Autosomal dominant endocrine adenomatosis. | Freckling; cerebral hemorrhage; tachycardia, congestive heart failure, hypertension; pheochromocytoma, islet cell tumor. | OMIM (171420) |
| **Pheochromocytoma** | Catecholamine-secreting tumors that usually arise within the adrenal medulla. | CALM; hemangiomata; cerebellar hemorrhage; renal artery stenosis, tachycardia, congestive heart failure; hypertension. | OMIM (171300) |
| **Adiposis dolorosa** | Generalized obesity. | Lipomas, CALM; chronic pain, fatigue, sleep disturbances; depression, anxiety, arthralgia; muscle aches. | OMIM (103200) Campen, 2001 |
| **Multiple endocrine neoplasia type I** | Tumors: parathyroid, pancreatic, duodenal endocrine cells; anterior pituitary adenomas. | Lipomas, collagenomas, CALM, hypopigmented macules; adenoma: parathyroid, adrenocortical; prolactinoma, gastrinoma, carcinoid tumors. | OMIM (131100) |
| **Multiple endocrine neoplasia type IIB** | Hamartoneoplastic syndrome characterized by aggressive medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, thickened colonic diverticula. | CALM; ganglioneuroma, myopathy, developmental delay; failure to thrive; parathyroid hyperplasia; goiter; colonic diverticulitis. | OMIM (162300) |

**Miscellaneous**

| Syndrome/Condition | Typical Signs | General Signs | Ref. |
|--------------------|--------------|--------------|-----|
| **Fanconi anemia (FANCA, FANCC, FANCD2, FANCI)** | Developmental abnormalities in major organ systems, early-onset bone marrow failure, high predisposition to cancer (leukemia). | Malformations: skeleton (small stature, radial aplasia, thumb deformity, vertebrae defects), skin (hyperpigmentation, CALM), urogenital, cardiopulmonary, gastrointestinal, central nervous systems. | ORPHA:84 OMIM(227650, 227645, 227646, 609053) |
| **Anemia, hypochromic microcytic, with iron overload** | Severe anemia requiring regular transfusions. | Erythropoietic hyperplasia of bone marrow. | OMIM (615234) |

H&N: Head & Neck; CALM(s): café-au-lait macule(s); OMIM: Online Mendelian Inheritance in Man; ORPHA: rare disease nomenclature.

Source: Authors.
Neurological disorders were observed in 32 types of diseases that present CALM, which may include a wide spectrum of changes, such as cognitive impairment, mental retardation, developmental delay, multiple aneurysms, cerebellar cortical degeneration, cerebellar ataxia, seizures, central nervous system malformations, brain tumors, hyperactivity, autistic spectrum disorders, peripheral nerve tumors, and other disturbances. Short stature was a characteristic observed in 28 of the identified genetic syndromes. Other relevant clinical findings observed in CALM-associated syndromes included predisposition to cancer (observed in 16 of 60 types of syndromes) and endocrine disturbances. Changes in the head and neck assessment were found in 52 syndromes linked to the presence of CALM.

The OMIM number, mode of inheritance, chromosome, mutated genes, and affected proteins for the 60 identified diseases that may exhibit CALM in their clinical presentation are listed in Table 2 (grouped according to mutated gene classification). The most common mode of inheritance for syndromes with CALM is autosomal dominant, occurring in 68.3% (41 of 60) of these genetic disorders. An autosomal recessive mode of inheritance was detected in 21.6% (13 of 60) of the syndromes, with the remainder being X-linked cases, isolated cases, or unestablished patterns of inheritance.

Table 2. Genetic syndromes reported with cafe-au-lait spots: genetics

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Logus syndrome | #611431 | AD   | 15q14 | SPRED1 | Sprouty-related, EVH1 domain-containing protein 1 |
| Neurofibromatosis type I | #162200 | AD   | 17q11.2 | NF1   | Neurofibromin                                |
| Leopard syndrome 1 | #151100 | AD   | 12q24.13 | PTPN11 | Tyrosine-protein phosphatase non-receptor type 11 |
| Leopard syndrome 2 | #611554 | AD   | 3p25.2 | RAF1   | RAF proto-oncogene serine/threonine-protein kinase |
| Watson syndrome | #193520 | AD   | 17q11.2 | NF1   | Neurofibromin                                |
| Noonan syndrome | #174800 | AD   | 12q13.32 | KITLG  | Kit ligand                                   |
| Noonan syndrome-like disorder with loose anagen hair 2 | #617506 | AD   | 2p23.2 | PPP1CB | Serine/threonine-protein phosphatase PP1-beta catalytic subunit |
| Noonan syndrome 6 | #613224 | AD   | 1p13.2 | NRAS   | GTPase NRas                                  |
| Cardiofaciocutaneous syndrome 1 | #115150 | AD   | 7q34 | BRAF   | Serine/threonine-protein kinase B-raf         |
| Costello syndrome | #218040 | AD   | 11p15.5 | HRAS   | GTPase HRas                                  |

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Familial progressive hyperpigmentation | #614233 | AD   | 19p13.3 | KITLG  | Kit ligand                                   |
| Familial progressive hyperpigmentation and hypopigmentation | #145250 | AD   | 12q21.32 | KITLG  | Kit ligand                                   |
| Piebald trait (piebaldism) | #172000 | AD   | 4q12 | KIT   | Mast/stem cell growth factor receptor Kit |
| Waardenburg syndrome type 2E | #611584 | AD   | 22q13.1 | SOX10  | Transcription factor SOX-10                  |

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Neurofibromatosis type II | #101000 | AD   | 22q12.2 | NF2   | Merlin                                        |
| McCune-Albright syndrome | #174800 | Sporadic | 20q13.32 | GNAS  | Guanine nucleotide-binding protein G subunit alpha isoform |
| Cowden syndrome 1 | #158350 | AD   | 10q23.31 | PTEN   | Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase |
| Peutz-Jeghers syndrome | #175200 | AD   | 19p13.3 | STK11  | Serine/threonine-protein kinase STK11          |

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Leopard syndrome | #613707 | AD   | 7q34 | BRAF   | Serine/threonine-protein kinase B-raf         |
| Leopard syndrome 3 | #601321 | AD   | 17q11.2 | NF1   | Neurofibromin                                |
| Neurofibromatosis-Noonan syndrome | #193520 | AD   | 17q11.2 | NF1   | Neurofibromin                                |
| Noonan syndrome-like disorder with loose anagen hair 2 | #617506 | AD   | 2p23.2 | PPP1CB | Serine/threonine-protein phosphatase PP1-beta catalytic subunit |
| Noonan syndrome 6 | #613224 | AD   | 1p13.2 | NRAS   | GTPase NRas                                  |
| Cardiofaciocutaneous syndrome 1 | #115150 | AD   | 7q34 | BRAF   | Serine/threonine-protein kinase B-raf         |
| Costello syndrome | #218040 | AD   | 11p15.5 | HRAS   | GTPase HRas                                  |

PHAKOMATOSES

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Neurofibromatosis type II | #101000 | AD   | 22q12.2 | NF2   | Merlin                                        |
| McCune-Albright syndrome | #174800 | Sporadic | 20q13.32 | GNAS  | Guanine nucleotide-binding protein G subunit alpha isoform |
| Cowden syndrome 1 | #158350 | AD   | 10q23.31 | PTEN   | Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase |
| Peutz-Jeghers syndrome | #175200 | AD   | 19p13.3 | STK11  | Serine/threonine-protein kinase STK11          |

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Leopard syndrome | #613707 | AD   | 7q34 | BRAF   | Serine/threonine-protein kinase B-raf         |
| Leopard syndrome 3 | #601321 | AD   | 17q11.2 | NF1   | Neurofibromin                                |
| Neurofibromatosis-Noonan syndrome | #193520 | AD   | 17q11.2 | NF1   | Neurofibromin                                |
| Noonan syndrome-like disorder with loose anagen hair 2 | #617506 | AD   | 2p23.2 | PPP1CB | Serine/threonine-protein phosphatase PP1-beta catalytic subunit |
| Noonan syndrome 6 | #613224 | AD   | 1p13.2 | NRAS   | GTPase NRas                                  |
| Cardiofaciocutaneous syndrome 1 | #115150 | AD   | 7q34 | BRAF   | Serine/threonine-protein kinase B-raf         |
| Costello syndrome | #218040 | AD   | 11p15.5 | HRAS   | GTPase HRas                                  |

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Familial progressive hyperpigmentation | #614233 | AD   | 19p13.3 | KITLG  | Kit ligand                                   |
| Familial progressive hyperpigmentation and hypopigmentation | #145250 | AD   | 12q21.32 | KITLG  | Kit ligand                                   |
| Piebald trait (piebaldism) | #172000 | AD   | 4q12 | KIT   | Mast/stem cell growth factor receptor Kit |
| Waardenburg syndrome type 2E | #611584 | AD   | 22q13.1 | SOX10  | Transcription factor SOX-10                  |

| Syndrome | OMIM#  | MOI  | Chromosome | Gene  | Protein                                      |
|----------|--------|------|------------|-------|----------------------------------------------|
| Neurofibromatosis type II | #101000 | AD   | 22q12.2 | NF2   | Merlin                                        |
| McCune-Albright syndrome | #174800 | Sporadic | 20q13.32 | GNAS  | Guanine nucleotide-binding protein G subunit alpha isoform |
| Cowden syndrome 1 | #158350 | AD   | 10q23.31 | PTEN   | Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase |
| Peutz-Jeghers syndrome | #175200 | AD   | 19p13.3 | STK11  | Serine/threonine-protein kinase STK11          |
Ataxia-telangiectasia  
Tuberous sclerosis 1  
Tuberous sclerosis 2  

**MISCELLANEOUS**

Adams-Oliver syndrome 4  
Carney complex  

| Syndrome                                        | OMIM#  | MOI | Chromosome  | Gene                  | Protein                                      |
|------------------------------------------------|--------|-----|-------------|-----------------------|----------------------------------------------|
| Bloom syndrome                                 | #210900 | AR  | 15q26.1     | RECQL3                | Bloom syndrome protein                       |
| Nijmegen breakage syndrome                     | #251260 | AR  | 8q21.3      | NBN                   | Nibrin                                       |
| Nijmegen breakage syndrome-Like disorder       | #613078 | AR  | 5q31.1      | RAD50                 | DNA repair protein RAD50                     |
| Microcephalic osteodysplastic primordial dwarfism type II | #210720 | AR  | 21q22.3     | PCNT                  | Pericentrin                                  |
| Johanson-Blizzard Syndrome                     | #243800 | AR  | 15q15.2     | UBR1                  | E3 ubiquitin-protein ligase UBR1             |
| Noonan syndrome 13                             | #619087 | AD  | 22q11.22    | MAPK1                 | Not reported                                 |
| Noonan Syndrome-like disorder with or without juvenile myelomonocytic leukemia | #613563 | AD  | 11q23.3     | CBL                   | E3 ubiquitin-protein ligase CBL              |
| Seckel syndrome 2                              | #606744 | AR  | 18q11.2     | RBBP8                 | DNA endonuclease RBBP8                       |
| Roberts syndrome                               | #268300 | AR  | 8p21.1      | ESCO2                 | N-acetyltransferase ESCO2                   |
| Mismatch repair cancer syndrome                | #276300 | AR  | 3p22.2      | MLH1                  | Protein Mlh1                                 |
|                                               |        |     |             | 2p21-1p16             | Protein Msh2                                 |
|                                               |        |     |             | 2p16                  | Protein Msh6                                 |
|                                               |        |     |             | 7p22                  | Endonuclease PMS2                            |
| Ohdo syndrome, X-linked                        | #300895 | XLR | Xq13.1      | MED12                 | Mediator of RNA polymerase II transcription subunit 12 |
| Autosomal recessive primary microcephaly       | #604804 | AR  | 9q33.2      | CDK5RAP2              | CDK5 regulatory subunit-associated protein 2 |
| Smith-Kingsmore syndrome                       | #616638 | AD  | 1p36.22     | MTOR                  | Serine/threonine-protein kinase mTOR         |
| Developmental delay, intellectual disability, obesity, and dysmorphism | #617991 | AD  | 14q14.1     | PHIP                  | PH-interacting protein                       |
| Ring chromosome 14 syndrome                    | #616606 | IC  | Chr.14      | RC14R                 | Not reported                                 |
| Genetic susceptibility to neuroblastoma        | #256700 | AD  | 14q23.3     | MAX                   | Protein max                                  |
| Multiple endocrine neoplasia type 1            | #131100 | AD  | 11q13.1     | MEN1                  | Menin                                        |
Multiple endocrine neoplasia type 2B #162300 AD 10q11.21 RET Proto-oncogene tyrosine-protein kinase receptor Ret

| Syndrome | OMIM# | MOI | Chromosome | Gene | Protein |
|----------|-------|-----|------------|------|---------|
| MISCELLANEOUS | | | | | |
| Pheochromocytoma | #171300 | AD | 1p36.22, 1p36.13 | KIF1B, SDHB | Kinesin-like protein KIF1B, Succinate dehydrogenase iron-sulfur subunit, mitochondrial |
| | | | 2q11.2, 3p25.3 | TMEM127, VHL | Transmembrane protein 127, Von Hippel-Lindau disease tumor suppressor |
| | | | 5p13.2 | GDNF | Glial cell line-derived neurotropic factor |
| | | | 10q11.21 | RET | Proto-oncogene tyrosine-protein kinase receptor Ret |
| | | | 11q23.1 | SDHD | Succinate dehydrogenase cytochrome b subunit mitochondrial |
| | | | 14q23.3 | MAX | Protein max |
| Silver-Russell syndrome 1 | #180860 | AD | 11p15.5 | ICR1 | Insulin-like growth factor II |
| Mulchandani-Bhoj-Conlin syndrome | #617352 | AD | 20q11-q13 | Not reported | Not reported |
| Fanconi anemia (FA), complementation group A | #227650 | AR | 16q24.3 | FANCA | FA group A protein |
| | #227645 | AR | 9q22.32 | FANCC | FA group C protein |
| | #69053 | AR | 15q26.1 | FANCI | FA group I protein |
| FA, group D2 | #227646 | AR | 3p25.3 | FANCD2 | FA group D2 protein |
| Anemia, hypochromic microcytic, with iron overload 2 | #615234 | AD | 2q14.2 | STEAP3 | Metalloreductase STEAP3 |

UNKNOWN GENES

| Syndrome | OMIM# | MOI | Chromosome | Gene | Protein |
|----------|-------|-----|------------|------|---------|
| Multiple cafe-au-lait spots | #114030 | AD | Unknown | Unknown | Unknown |
| Gastrocutaneous syndrome | #137270 | AD | Unknown | Unknown | Unknown |
| Neurofibromatosis type III | #162260 | AD | Unknown | Unknown | Unknown |
| Russell-Silver syndrome, X-linked | #312780 | X-linked | Chromosome X | Unknown | Unknown |
| Turner syndrome | ORPHA 881 | X-linked | Chromosome X | Unknown | Unknown |
| Johnson neuroectodermal syndrome | #147770 | AD | Unknown | Unknown | Unknown |
| Pheochromocytoma-islet cell tumor syndrome | #171420 | AD | Unknown | Unknown | Unknown |
| Adiposis dolorosa | #103200 | AD/sporadically | Unknown | Unknown | Unknown |

Source: Authors.

4. Discussion

Genetic disorders account for approximately 80% of all rare diseases (Giugliani et al., 2019). All syndromes associated with the presence of CALM listed here are rare. There is no single definition for rare diseases. Within health systems, rare diseases have been defined based on the criteria of prevalence or number of affected individuals. According to the European Union, rare diseases are defined as those that affect less than 1 in 2,000 people (Giugliani et al., 2019). For the World Health Organization, a rare disease is one that affects up to 65 people in 100,000 individuals or 1.3 people in every 2,000 individuals. In the United States, legislation defines rare diseases strictly according to prevalence, specifically as “any disease or condition that affects fewer than 200,000 people in the United States”. Brazil follows the same definition of rare diseases adopted by the World Health Organization (Alawi, 2019; Martelli, 2019).

Among all identified syndromes, neurofibromatosis type 1 is the most common, with a worldwide incidence ranging from 1 in 2,500 to 1 in 3,000 individuals (OMIM). It is the disease in which the association with CALM is well-recognized and considered a diagnostic hallmark (Shah, 2010; Zhang et al., 2016). However, in the presence of early-onset and multiple CALMs, several other genetic syndromes should be excluded (but not limited to), such as neurofibromatosis type II (Ferner, 2007; Evans, 2009; Madson, 2012; Plana-Pla, Bielsa-Marsol & Carrato-Monino, 2017; Hamm et al., 2019), neurofibromatosis type III (Madson, 2012), Legius syndrome (neurofibromatosis type 1-like syndrome) (Madson, 2012; Zhang et al., 2016),
multiple cafe-au-lait spots (Orphanet; Madson, 2012), McCune-Albright syndrome (Shah, 2010; Madson, 2012; Hamm et al., 2019), Noonan syndrome (Madson, 2012), Leopard syndrome (Madson, 2012; Zhang et al., 2016; Hamm et al., 2019), gastrocutaneous syndrome (Hamm et al., 2019), familial progressive hyperpigmentation and hypopigmentation (Amyere et al., 2011), familial progressive hyperpigmentation (Zhang et al., 2016), mismatch repair cancer syndrome (Shah, 2010; Baas et al., 2013; Hamm et al., 2019), Watson syndrome (Madson, 2012; Hamm et al., 2019) and cardiofaciocutaneous syndrome 1 (Hamm et al., 2019).

Most of these diseases that present multiple CALMs are part of the developmental diseases known as RASopathies. These diseases, which are associated with germline genetic modifications, comprise a group of clinically and genetically related diseases that present mutations and deletions associated with protein-coding genes that lead to activation and/or dysregulation of the Ras/mitogen-activated protein kinase (RAS/MAPK) pathway (Tajan, Paccoud, Branks, Edouard, & Yart, 2018). Neurofibromatosis type I is caused by loss-of-function mutations of the NF1 gene that encodes neurofibromin (Picardo & Cardinali, 2011); Legius syndrome results from inactivating mutations in the SPRED1 gene (Zhang et al., 2016; Tajan et al., 2018); Noonan syndrome caused by mutations in PTPN11, SOS1, RAFI, KRAS, NRAS, BRAF, RIT1, and RRAS genes (Zhang et al., 2016; Cao, Alrejaye, Klein, Goodwin & Oberol, 2017; Tajan et al., 2018); Leopard syndrome, due to mutations in PTPN11, RAF1, and BRAF genes (Hamm et al., 2019); Costello syndrome due to activating mutations in the HRAS gene (Aoki, Niihori, Inoue & Matsubara, 2016; Zhang et al., 2016); cardiofaciocutaneous syndrome resulting from gain-of-function mutations in the BRAF, KRAS, and MAP2K1 or MAP2K2 genes (Digilo et al., 2011; Aoki et al., 2016; Zhang et al., 2016); and Noonan-like syndrome with loose anagen hair after mutations in the SHOC2 or PPP1CB (Tajan et al., 2018). New gene research tools have led to a better understanding of the complexity of RAS signaling and consequently to an expansion of the pathogenic etiology of RASopathies. In this context, the genes identified that represent novel genes causative for RASopathy include the RIT1, SOS2, RASA2, RRAS, and SYNGAP1 genes (Tidyman & Rauen, 2016). The RAS/MAPK pathway has been shown to be the predominant biochemical hallmark of the RASopathies. However, aberrant Ras signaling due to other effector pathways also appears to play an important role (Tidyman & Rauen, 2016).

Piebaldism, Waardenburg syndrome and peripheral demyelinating neuropathy-central dysmyelinating- Waardenburg syndrome-Hirschsprung disease (PCWH) are genetic disorders secondary to aberrant melanoblast migration during embryogenesis (Oiso et al., 2013). The binding of the KIT ligand (KITLG) to its KIT tyrosine kinase receptor, that triggers the Ras/mitogen-activated protein kinase signaling pathway, regulates melanocyte migration, differentiation and survival, as well as cell proliferation, melanogenesis and melanosome transfer (Oiso et al., 2013). Among these reported diseases, piebaldism (Zhang et al., 2016) and Waardenburg syndrome type 2E may present CALM as a clinical manifestation. Other disorders related to the KITLG / KIT signaling pathway that may also have CALM are familial progressive hyperpigmentation and hypopigmentation (FPHH) and familial progressive hyperpigmentation (FPH) (Oiso et al., 2013; Zhang et al., 2016).

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 (Sarnat & Flores-Sarnat, 2005; Gursoy & Erçal, 2018). This group includes pathologies with different genetic mechanisms (Sarnat & Flores-Sarnat, 2005; Klar, Cohen & Lin, 2016). So we have neurofibromatosis type I that exhibits mutations in the NF1 gene, which encodes neurofibrin, a negative regulator of RAS signaling that is also expressed in migrating neural crest cells during early fetal development; neurofibromatosis type II, where mutations occur in the NF2 gene that encodes a 595 amino acid protein, named Merlin, a negative Schwann cell regulator whose impairment allows Schwann cells to proliferate excessively; tuberous sclerosis complex, where mutations in the TSC1 and TSC2 genes are responsible for the pathogenesis of the disease, leading to overactivation of the mTOR pathway, which plays an essential role in normal cell growth, proliferation, and survival (Gursoy & Erçal, 2018). They usually involve inherited conditions, but spontaneous mutations can occur. As a common feature in the group,
all diseases represent neurocristopathies and therefore share a common ectodermal embryologic origin, include abnormalities in the tissues of ectodermal origin, especially skin, eyes, and central nervous system (Reith, 2013). However, it is significant to emphasize that the neural crest is also important as an inducer of many tissues in craniofacial development and other mesodermal structures (Sarnat & Flores-Sarnat, 2005). Neurofibromatosis type I, neurofibromatosis type II, tuberous sclerosis, ataxia-telangiectasia, Peutz-Jeghers syndrome, McCune-Albright syndrome and Cowden syndrome 1 are diseases belonging to this group that have CALM as a phenotypic manifestation.

In addition to these classifications, localized or general melanotic hyperpigmentation may be part of the clinical presentation of many other congenital systemic disorders that result from ubiquitous protein defects and/or basal cell processes (Baxter & Pavan, 2013). This suggests that melanocytes are a cell type with high sensitivity to such disorders. A representative example is Fanconi anemia, a genetically heterogeneous disorder that affects DNA repair, characterized by different phenotypes that affect all organ systems (Baxter & Pavan, 2013).

Among all characteristics of these hereditary syndromes associated with CALM, predisposition to tumors is one of the most important, considering the high levels of cancers associated with these syndromes, with many of these cancers presenting in childhood (Walsh et al., 2017). The incidence of specific types of cancer in the carriers of the germline mutations is dramatically high compared to the general population, considering that the rate of a simple somatic allelic loss is exponentially greater than the independent mutation of two alleles within the same cell (Elissen, 2016). Malignant tumors are the most common cause of death in individuals with some of these familial tumor syndromes (Brems, Beert, Ravel & Legius, 2009).

The trend to develop tumors, which was observed in 16 of the 60 syndromes listed in this study, suggests a common underlying genetic basis. In this line, in neurofibromatosis type 1, the NF1 gene acts as a tumor suppressor gene (Origone et al., 2003). In this condition, a germline pathogenic variant and a somatic mutation lead to homozygous inactivation of the NF1 gene, resulting in a partial or total interruption of neurofibromin activity causing increased intracellular RAS signaling and abnormal cell proliferation (Origone et al., 2003). Different mechanisms are involved in the somatic inactivation observed in these hereditary syndromes, such as intragenic mutations (eg, nonsense, missense, frameshift, splice-site mutations, small insertions, and deletions), loss of heterozygosity, and hypermethylation of the promoter (Brems et al., 2009).

Another example is the genetically proven constitutional mismatch repair deficiency syndrome (CMMRD), a disease with multiple CALMs and other features of NF1 that are also part of the clinical findings. It is speculated that the remaining NF1 signals in patients with CMMRD result from post-zygotic mutations of the NF1 gene that may occur more frequently than normal in the population due to an accelerated rate of NF1 mutation in cells without a functional MMR system. However, it is also possible that CALM and other NF1 resources in these patients represent "isolated" skin manifestations (Maertens et al., 2007; Wimmer et al., 2017). Ataxia telangiectasia, Bloom syndrome, Nijmegen rupture syndrome and Fanconi anemia are among the most common DNA repair diseases and may present with CALM (Walsh et al., 2017). Pathogenic germline mutations in genes encoding proteins key in DNA repair and telomere biology result in the characteristic physical findings observed in patients with these hereditary disorders and in a high risk of cancer associated with these syndromes (Walsh et al., 2017).

5. Conclusion

The presence of CALM during a clinical evaluation of a patient should always be critically assessed by the healthcare professional, who must be aware of the possibility of an associated genetic syndrome. A detailed clinical evaluation should be performed by the physician to identify signs and symptoms that indicate the presence of any systemic disease.
If a genetic syndrome is suspected, given the genetic complexity and phenotypic heterogeneity of diseases that present CALM, the large number of overlapping features in similar diseases, and the incurable nature of these conditions, advanced testing is needed to distinguish between these syndromes, to provide genetic counseling to families, establish the prognosis and available therapeutic measures, monitor the potential risk to prevent complications.

It is important to note that, although the vast majority of genetic syndromes meet the criteria for a rare disease, it is estimated that there are between 6,000 and 8,000 different types of rare diseases described, with consequently millions of people affected by these diseases worldwide. The specific diagnosis of the genetic syndrome that affects a given patient has a great impact on their life, both in terms of clinical guidance and early treatment, and in the emotional sense, as it provides some comfort by obtaining an explanation for their symptoms, in addition to the possibility of obtaining support from groups of people affected by the same disease. Thus, research that systematizes knowledge on a given topic and organizes clinical signs and symptoms into a coherent system, as done in this study, can provide valuable tools in the process of building clinical reasoning and can add value to clinical practice, contributing to improved clinical outcomes.

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