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Encephalocraniocutaneous Lipomatosis

Synonyms: Fishman Syndrome, Haberland Syndrome

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Summary

Clinical characteristics

Encephalocraniocutaneous lipomatosis (ECCL) comprises a spectrum of predominantly congenital anomalies. In its typical form, ECCL is characterized by congenital anomalies of the skin (nevus psiloliparus, patchy or streaky non-scarring alopecia, subcutaneous lipomas in the frontotemporal region, focal skin aplasia or hypoplasia on the scalp, and/or small nodular skin tags on the eyelids or between the outer canthus and tragus), eye (choristoma), and brain (in particular intracranial and spinal lipomas). To a much lesser degree, the bones and the heart can be affected. About 40% of affected individuals have bilateral abnormalities of the skin or the eyes. About one third of affected individuals have normal cognitive development, another one third have mild developmental delay (DD) or intellectual disability (ID), and the final one third have severe or unspecified DD/ID. Half of individuals have seizures. Affected individuals are at an increased (i.e., above the general population) risk of developing brain tumors, particularly low-grade gliomas such as pilocytic astrocytomas. There is evidence that oculoectodermal syndrome (OES) may constitute a clinical spectrum with ECCL, with OES on the mild end and ECCL on the more severe end of the spectrum.

Diagnosis/testing

A clinical diagnosis of ECCL can be made in individuals with:

- Involvement of at least three systems, with major criteria in at least two of the three systems; **OR**
- Involvement of at least three systems, in which one major criterion is either a biopsy-proven nevus psiloliparus (NP) OR a possible NP with at least one other minor skin criterion; **OR**
- At least one major criterion in each of two systems, where one major criterion is either a biopsy-proven NP or a possible NP with at least one other minor skin criterion.

A molecular diagnosis can be established in a proband with suggestive findings and a mosaic activating pathogenic variant identified in either *FGFR1* or *KRAS*. Due to the mosaic nature of the condition, molecular

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genetic testing on DNA derived from affected tissue has the best detection rate and molecular methods that can detect low levels of mosaicism are recommended.

Management

Treatment of manifestations: Standard treatment for skin manifestations (when appropriate; most of the skin findings do not require active management), choristomas / eye anomalies (including community vision services, as needed), low-grade gliomas, DD/ID, and jaw/dental anomalies; standard treatment with anti-seizure medication for those with epilepsy; standard treatment of Wilms tumor per oncologist.

Surveillance: Assess for new neurologic manifestations (changes in tone, seizures), developmental progress, and educational needs at each visit; dental evaluation at least every six months; unless the individual has molecularly confirmed *KRAS*-related ECCL, consider performing brain MRI to screen for brain tumors annually or as clinically indicated; ophthalmologic evaluations annually in childhood and adolescence or as clinically indicated; consideration of renal ultrasound every three months until age eight years to screen for Wilms tumor in those who have a *KRAS* pathogenic variant that involves codon 12.

Genetic counseling

ECCL is not known to be inherited. No confirmed vertical transmission or sib recurrence has been reported. Given the postzygotic mutational mechanism of ECCL, the risk for an affected sib would be expected to be the same as in the general population.

Diagnosis

Clinical diagnostic criteria for encephalocraniocutaneous lipomatosis (ECCL) have been published [Moog 2009] and are adapted below based on the recent literature (see Establishing the Diagnosis).

Suggestive Findings

ECCL **should be suspected** in individuals with at least one major criterion in each of two different systems or in individuals with a biopsy-proven or possible nevus psiloliparus (NP), and one minor criterion in a second (non-skin) system (for clinical diagnostic criteria, see Clinical Diagnosis).

Major Criteria

Skin

- Biopsy-proven nevus psiloliparus (NP) (Figure 1)
- Possible NP in addition to one or more of the other minor skin criteria listed below
- Two or more minor skin criteria listed below

Eye. Choristoma (e.g., epibulbar dermoid) (Figure 2C)

Central nervous system (CNS)

- Intracranial lipoma (Figure 3)
- Intraspinal lipoma (Figure 4)
- Low-grade glioma (if associated with other suggestive findings)
- Two minor CNS criteria listed below

Other

- Jaw tumor (osteoma, odontoma, or ossifying fibroma) (Figure 5)
- Multiple bone cysts (Figure 6)

- Aortic coarctation

Minor Criteria

Skin

- Possible NP
- Patchy or streaky non-scarring alopecia (without fatty nevus) (Figure 2A, 2B)
- Subcutaneous lipoma(s) in the frontotemporal region (Figure 2B, 2C, and Figure 7)
- Focal skin aplasia/hypoplasia on the scalp
- Small nodular skin tags on the eyelids or between outer canthus and tragus

Eye

- Corneal and other anterior chamber anomalies
- Ocular or eyelid coloboma
- Calcification of the globe

CNS

- Abnormal intracranial vessels (e.g., angioma, excessive vessels)
- Arachnoid cyst or other abnormality of meninges
- Complete or partial atrophy of a hemisphere
- Porencephalic cysts(s)
- Asymmetrically dilated ventricles or hydrocephalus
- Calcification not involving the basal ganglia

Establishing the Diagnosis

The clinical diagnosis of ECCL can be **established** in a proband based on clinical diagnostic criteria [Moog 2009], or the molecular diagnosis can be established in a proband with suggestive findings (i.e., findings consistent with ECCL as noted above but not sufficient to meet the clinical diagnostic criteria for ECCL) and a mosaic activating pathogenic variant in either *FGFR1* or *KRAS* identified by molecular genetic testing (see Table 1).

Clinical Diagnosis

A clinical diagnosis can be made in an individual with:

- Involvement of at least three systems, with major criteria in at least two out of the three systems; **OR**
- Involvement of at least three systems, in which one major criterion is either a biopsy-proven NP OR a possible NP with at least one other minor skin criterion; **OR**
- At least one major criterion in each of two systems, where one major criterion is either a biopsy-proven NP OR a possible NP with at least one other minor skin criterion.

Molecular Diagnosis

Molecular genetic testing approaches typically include use of **gene-targeted testing** (single-gene testing, multigene panel), although **comprehensive genomic testing** (exome sequencing, genome sequencing) is available. Because all reported *FGFR1* or *KRAS* pathogenic variants are postzygotic (and thus mosaic), more than one tissue (excluding blood, buccal swabs, and saliva) may need to be tested.

- Experience suggests that sequence analysis of DNA derived from affected tissue has the best detection rate with the highest levels detected in fibroblast culture derived from skin overlying nevus psiloliparus, non-ossifying fibromas, and dermoids. Pathogenic variants have been detected in DNA derived from skin

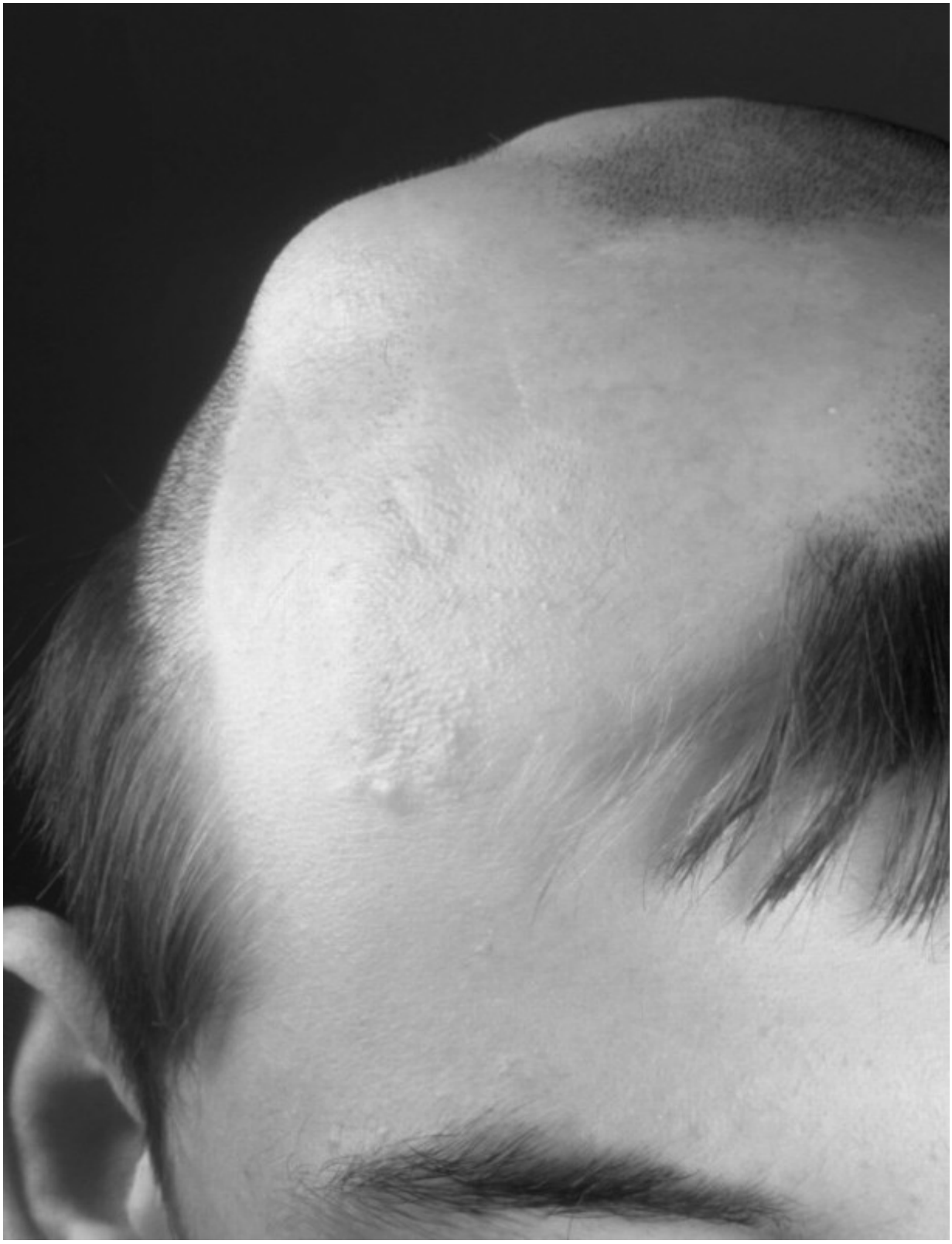

Figure 1: Nevus psiloliparus: a smooth hairless fatty tissue nevus on the scalp
Reproduced with permission from Moog [2009]

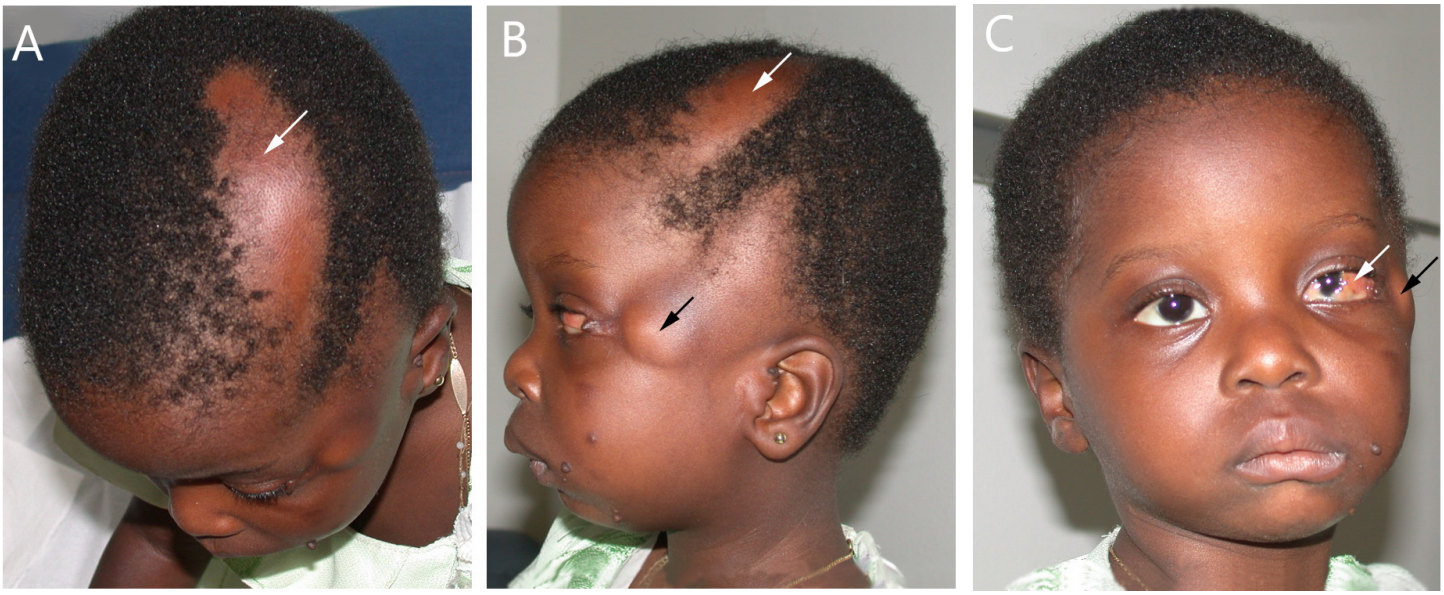

Figure 2. Linear alopecia (white arrows in A and B) and choristoma (C) in an affected individual age 2.5 years. Note overgrowth of the left lower face and epibulbar dermoid (white arrow in C), subcutaneous fatty masses (black arrows in B and C) and small nodular skin tags, both extending to the canthus.

Adapted with permission from Moog et al [2007a]

biopsy-based fibroblast cultures; however, the impact of cell culture on pathogenic variant levels remains uncertain. DNA directly obtained from these tissues, without culture, should be prioritized for genetic testing.

- Intermediate levels of somatic pathogenic variants have been detected in lipoma, bone, and non-affected skin, but these should be used primarily when biopsies of higher-yield lesions are not available.
- The level of mosaicism for an activating variant in skin is variable, whether a lesion (aplasia, alopecia, or hyperpigmentation) is seen or not.
- Sequence analysis of DNA from blood, buccal swabs, and saliva has been uniformly normal (i.e., it did not identify a mosaic-activating pathogenic variant) – with the exception of one individual in whom ultra-deep sequencing by digital droplet PCR (ddPCR) detected a pathogenic variant allele fraction (level of mosaicism) at or below 1% [Kordacka et al 2019]. Thus, these tissues should be avoided for sequencing.

Note: On analysis of DNA derived from affected tissues, the method used for testing must be sensitive enough to detect low-level mosaicism of a pathogenic variant (see Molecular Pathogenesis, **Gene-specific laboratory technical considerations**).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those in whom the diagnosis of ECCL has not been considered **may** be diagnosed using genomic testing (see **Option 2**), if an appropriate sample is used.

Option 1

When the phenotypic findings suggest a diagnosis of ECCL, molecular genetic testing approaches can include use of a **multigene panel** that includes both *FGFR1* and *KRAS*, or less often, **serial single-gene testing.**

- **A multigene panel** that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) on an appropriate sample (see preceding) may be considered. Note: (1) The genes included in

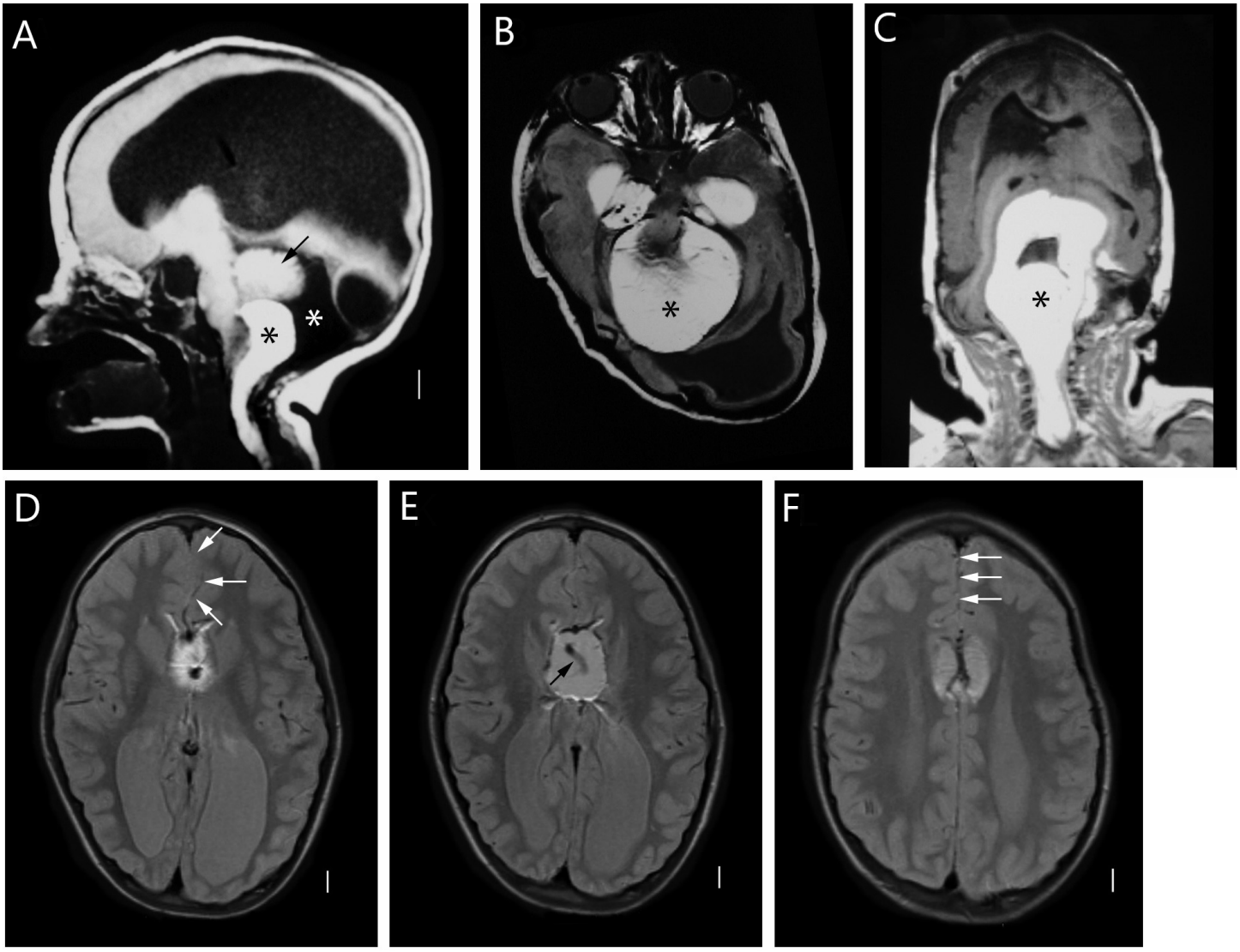

Figure 3. Brain and spinal cord MRI in two individuals with ECCL

Images from one affected individual (A–C) demonstrate hydrocephalus (A), moderate cerebellar vermis hypoplasia with large fluid collections or cysts behind and below the vermis (white asterisk in A), and a massive midline lipoma extending from several centimeters above the cerebellum, around the cerebellum and brain stem and down into the spinal cord (black asterisks in A, B, and C). Adjacent structures such as the thalamus and hypothalamus are deviated upwards and outwards by the lipoma.

Images from another affected individual (D–F) show a large lipoma of the corpus callosum containing a large dysplastic vessel in the middle (black arrow in E) and deficiency of the anterior falx (D and F). The latter is suggested by close apposition and inappropriate interdigitation of the mesial frontal gyri at lower levels (offset white arrows in D) compared to higher levels (linear white arrows in F).

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the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

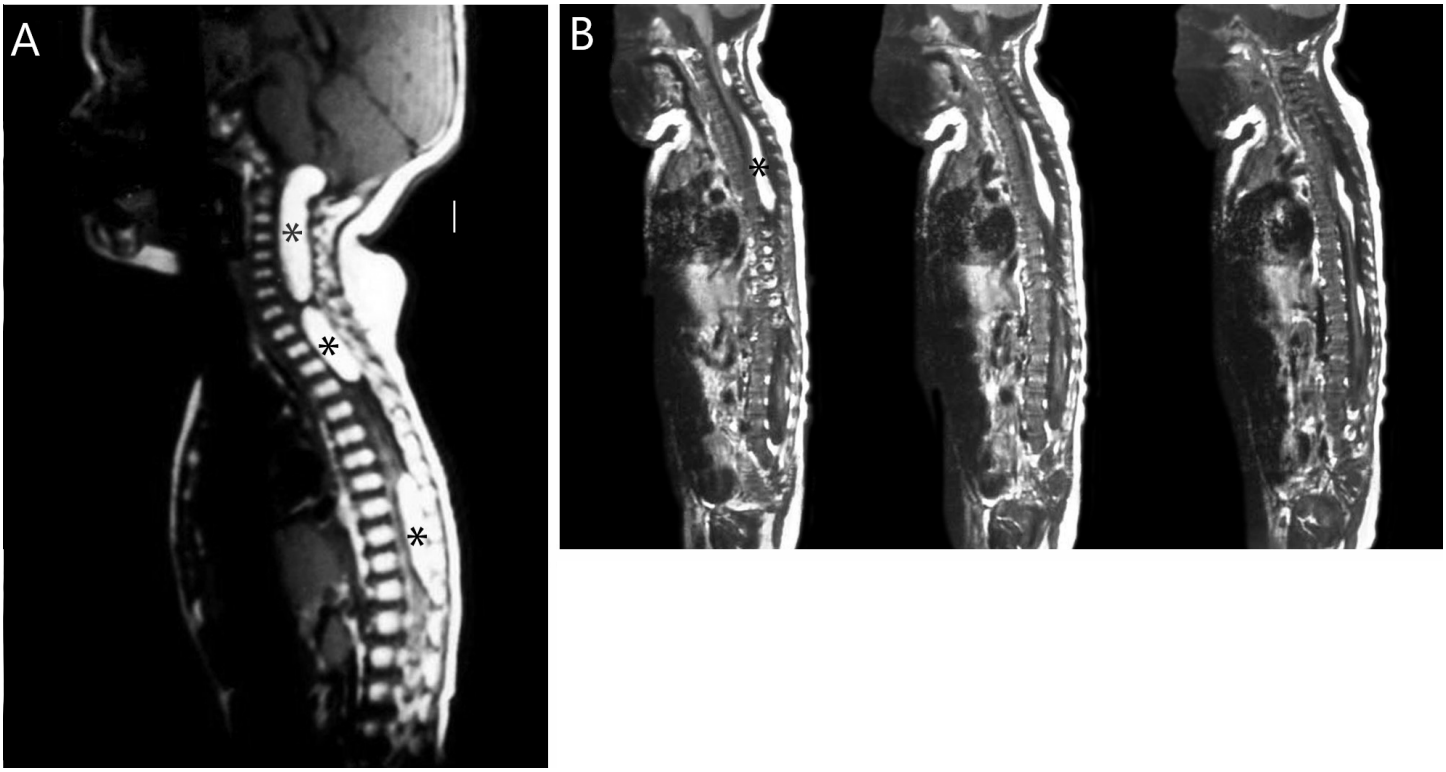

Figure 4. Brain and spinal cord MRI in ECCL

An image from one affected individual (A) shows several large lipomas ventral to the spinal cord (black asterisks) and a subcutaneous nuchal fatty mass.

Images from another affected individual (B) demonstrate lipomatosis along the full length of the spinal cord (asterisk and other areas).

Adapted with permission from Moog et al [2007a]

- **Serial single-gene testing.** Because the mosaic-activating pathogenic variants in *FGFR1* and *KRAS* are restricted to a few specific variants, targeted genetic testing for known mosaic-activating variants in *FGFR1*, followed by *KRAS*, may be considered (see Molecular Genetics). However, sequence analysis of both *FGFR1* and *KRAS* is also available.

Notes: (1) The mosaic pathogenic variants observed in both *FGFR1* and *KRAS* have all been associated with gain of function, so gene-targeted deletion/duplication analysis is not recommended. (2) Failure to detect an activating *FGFR1* or *KRAS* pathogenic variant does not exclude a diagnosis of ECCL in individuals who meet the clinical diagnostic criteria, given that a low level of mosaicism is observed in many affected individuals. Indeed, far more affected individuals have a clinical diagnosis of ECCL than a diagnosis established by molecular genetic testing.

Option 2

When the diagnosis of ECCL has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** on an appropriate sample (see above) may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

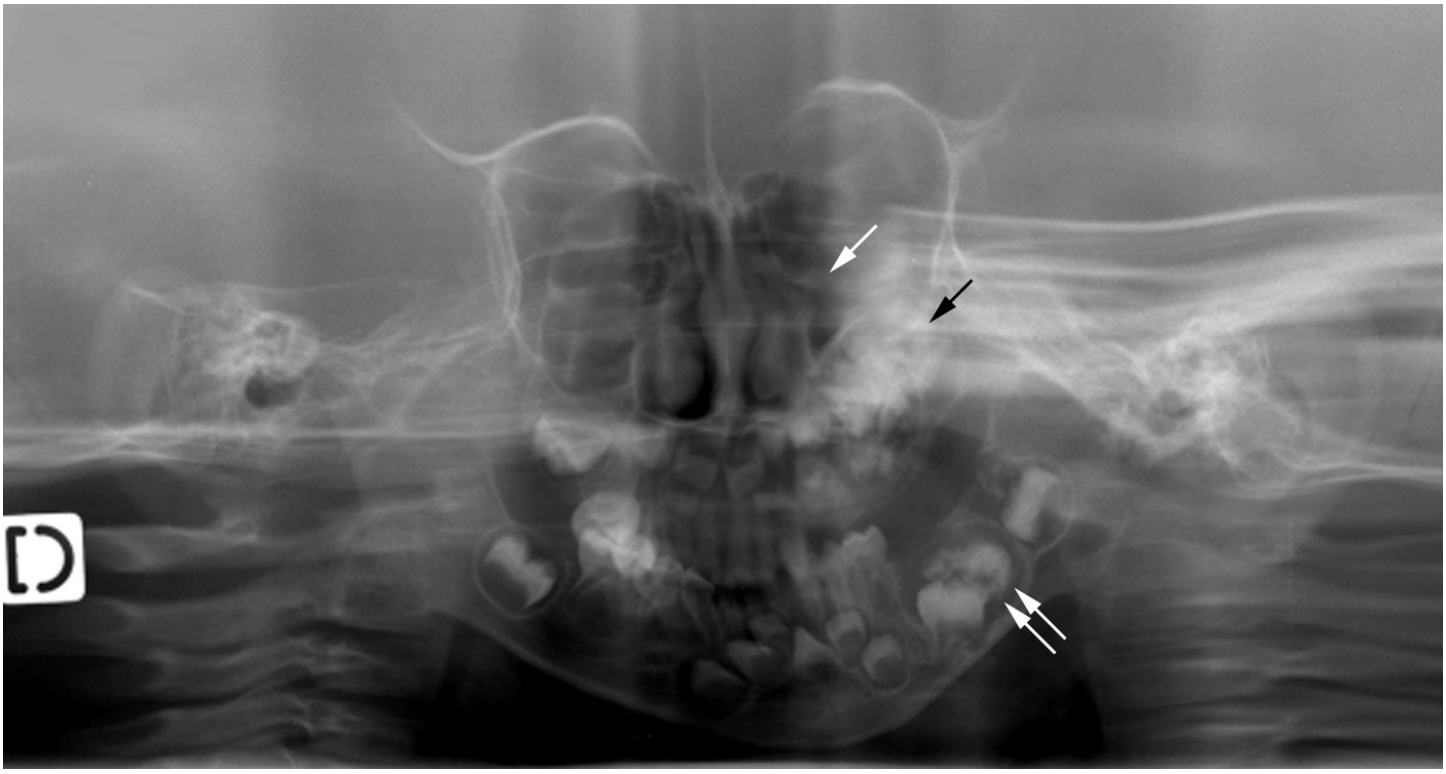

Figure 5. Panoramic radiographs of an affected individual showing hypoplasia of the left maxillary sinus (single white arrow), a bulky mass of dentine structures consistent with left maxillary odontomas (black arrow), and a solitary odontoma of the left lower jaw incorporating misshaped dental structures (double white arrows). Deciduous teeth in the lower jaw and teeth buds in the right maxilla are normal.

Adapted with permission from Moog et al [2007a]

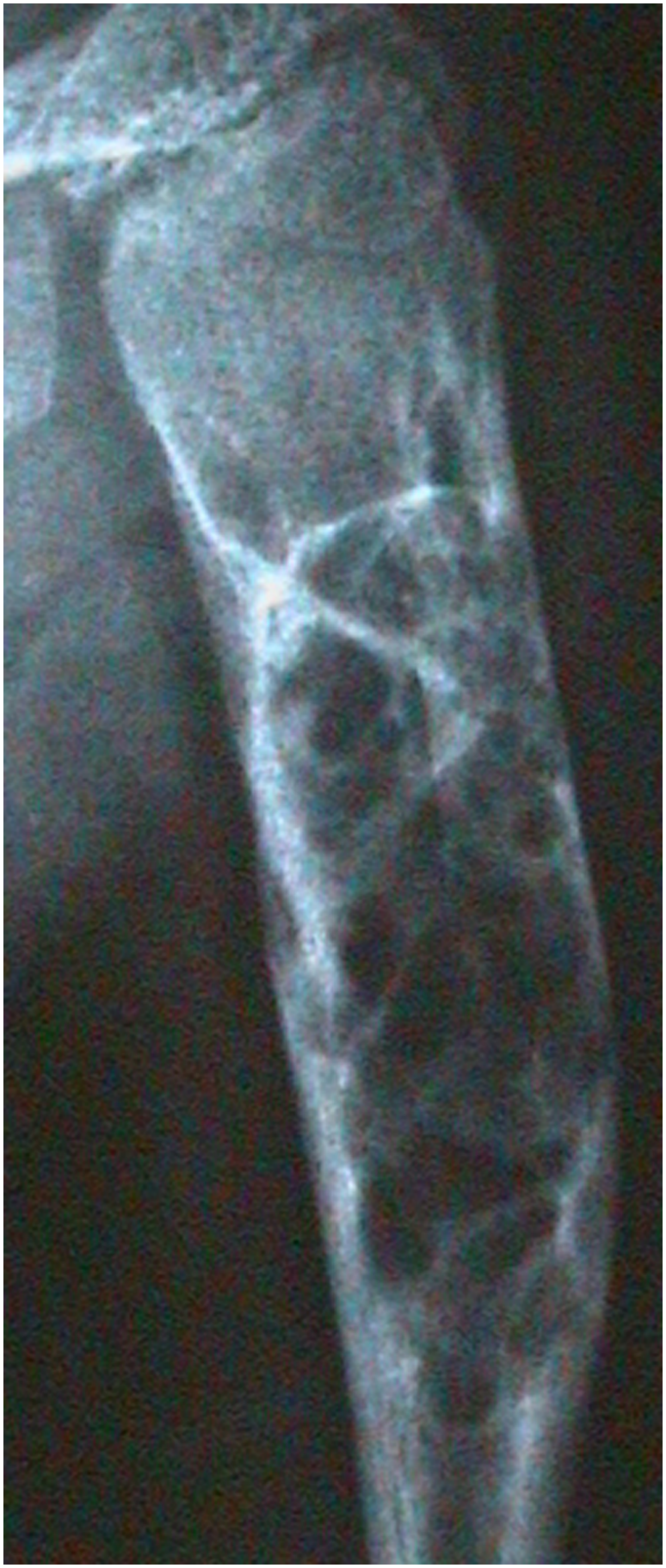

Figure 6. Multiple lytic bone lesions in the humerus

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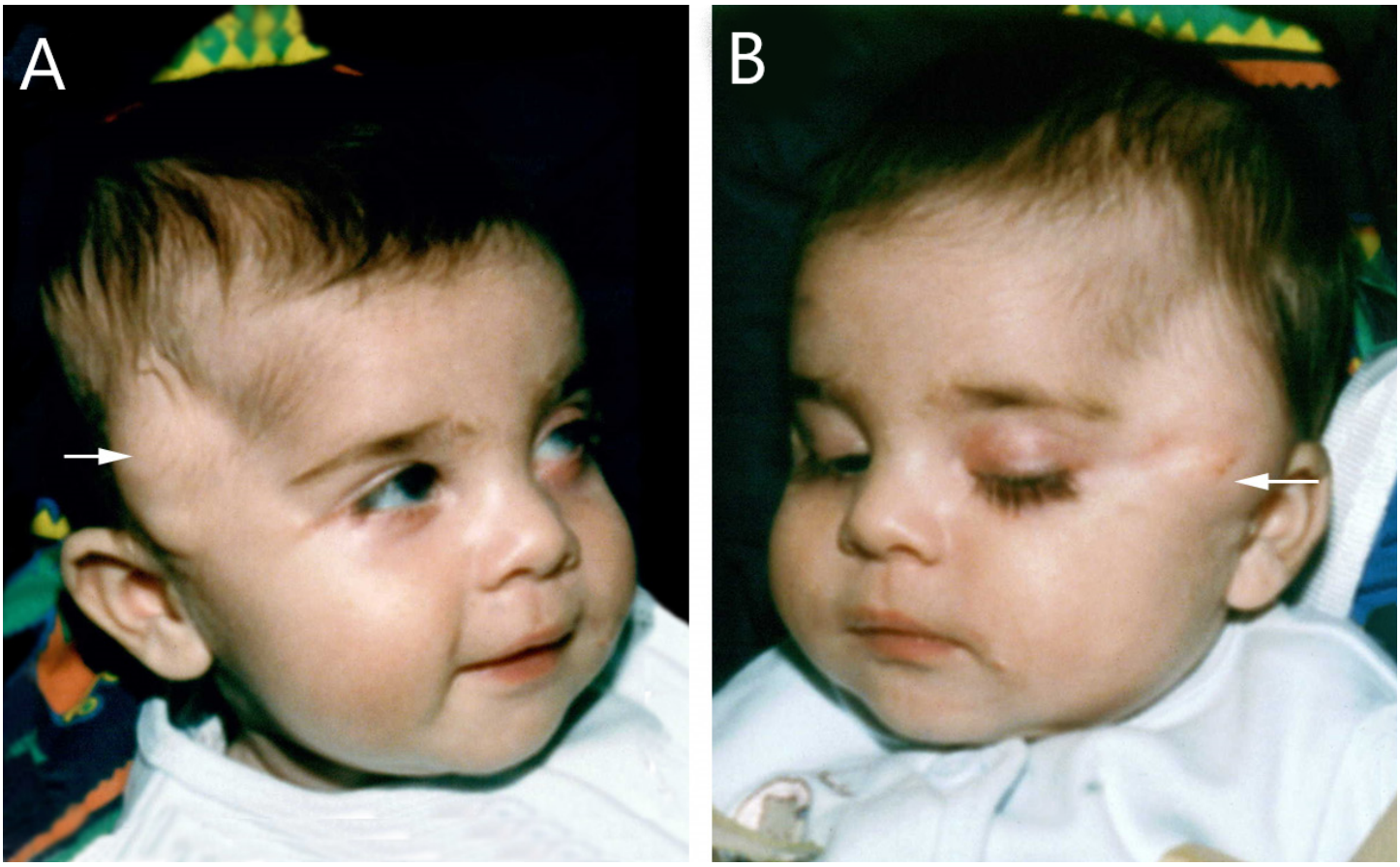

Figure 7. An affected individual age 5 months. Note the bilateral subcutaneous fatty accumulations (white arrows).
Adapted with permission from Moog et al [2007a]

Table 1. Molecular Genetic Testing Used in Encephalocraniocutaneous Lipomatosis

Gene [1, 2]	Proportion of ECCL Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Targeted variant analysis	Sequence analysis [4]
FGFR1	14/25 (56%) [5]	Unknown [6, 7]	See footnote 8.

Table 1. continued from previous page.

Gene [1, 2]	Proportion of ECCL Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Targeted variant analysis	Sequence analysis [4]
KRAS	11/25 (44%) [9, 10]	Unknown [7, 11]	See footnote 8.

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Bennett et al [2016], Bavle et al [2018], Valera et al [2018], Chacon-Camacho et al [2019], Córdoba et al [2019], Kordacka et al [2019]
6. The specific pathogenic variants in *FGFR1* that are known to cause ECCL are c.1638C>A (p.Asn546Lys) and c.1966A>G (p.Lys656Glu) (see Molecular Genetics).
7. Due to the somatic mosaic nature of ECCL, the actual detection rate depends on the sample provided, the molecular genetic testing method used, and the targeted variants evaluated. However, targeted variant analysis has the potential to detect the specific pathogenic variants listed in footnote 6 for *FGFR1* and in footnote 11 for *KRAS*.
8. Sequence analysis should detect all of the pathogenic variants detectable by targeted variant analysis, although sequence analysis may also detect other pathogenic variants that are causative of other phenotypes (see Genetically Related Disorders) or variants of unknown clinical significance.
9. The numbers include four individuals with an ECCL phenotype [Boppudi et al 2016, McDonell et al 2018, Chacon-Camacho et al 2019, Nagatsuma et al 2019] and seven individuals with an OES phenotype [Peacock et al 2015, Boppudi et al 2016, Chacon-Camacho et al 2019]. Note: Based on the diagnostic criteria above, a person who has suggestive findings and an identifiable pathogenic variant in *KRAS* can be given a diagnosis of ECCL even if they do not meet the full clinical diagnostic criteria for ECCL.
10. It is controversial whether OES is within the spectrum of ECCL. Some individuals who have a clinical diagnosis of OES do not meet the clinical diagnostic criteria for ECCL and do not have an identifiable pathogenic variant in KRAS, and therefore do not meet either diagnostic criteria for ECCL. However, this could be because molecular genetic testing for ECCL is challenging due to the mosaic nature of the pathogenic variant. Some individuals diagnosed with OES have pathogenic variants in NRAS (see Differential Diagnosis).
11. The specific pathogenic variants in *KRAS* known to cause ECCL are c.35G>A (p.Gly12Asp), c.38G>A (p.Gly13Asp), c.57G>C (p.Leu19Phe), c.436G>A (p.Ala146Thr), and c.437C>T (p.Ala146Val) (see Molecular Genetics).

Clinical Characteristics

Clinical Description

To date, at least 85 individuals with a clinical and/or molecular diagnosis of encephalocraniocutaneous lipomatosis (ECCL) have been reported [Moog 2009, Bennett et al 2016, McDonell et al 2018, Valera et al 2018]. Of these, 14 individuals have been identified with a pathogenic variant in *FGFR1* [Bennett et al 2016, Bavle et al 2018, Valera et al 2018, Chacon-Camacho et al 2019, Córdoba et al 2019, Kordacka et al 2019] and a few with a pathogenic variant in *KRAS* [Boppudi et al 2016, McDonell et al 2018, Chacon-Camacho et al 2019, Nagatsuma et al 2019]. The following description of the phenotypic features in individuals with a clinical and/or molecular diagnosis associated with ECCL is based on these reports.

Note: There is evidence that oculoectodermal syndrome (OES) may constitute a clinical spectrum with ECCL, with OES on the mild end and ECCL on the more severe end of the spectrum. Individuals who do not fulfill the clinical diagnostic criteria for ECCL but display some features have sometimes been reported as having OES (see Nomenclature).

ECCL comprises a spectrum of predominantly congenital anomalies. In its typical form, ECCL is characterized by congenital skin, eye, and brain anomalies, in particular intracranial and spinal lipomas. To a much lesser degree, the bones and the heart can be affected. About 40% of affected individuals have bilateral abnormalities of the skin or the eyes. Although variable in its extent and severity, the pattern of skin and eye findings is often consistent and recognizable.

Since 2016, ECCL has also been recognized as a tumor predisposition syndrome [Bennett et al 2016].

Table 2. Encephalocraniocutaneous Lipomatosis: Frequency of Select Features

Feature		% of Persons w/Feature	Comment
Skin	Nevus psiloliparus	75%	
	Nodular skin tags	70%-75%	Periocular or between outer canthus & tragus
	Alopecia	Common	A specific percentage is difficult to define.
	Subcutaneous fatty lipomas	40%	Frontotemporal or zygomatic
	Focal scalp aplasia/hypoplasia	25%	
	Pigmentary abnormalities	Rare	Either as spots or following lines of Blaschko
Eye	Choristomas	80%-85%	
CNS	Intracranial lipomas	65%	Often in cerebello-pontine angle
	Other findings	Common	See Table 3.
Neurologic	Developmental delay / intellectual disability	65%	
	Seizures	50%	
Tumors	Brain tumors	Unknown	Mostly low-grade glioma
	Jaw tumors	Unknown	

Based on Moog et al [2007a], Moog [2009], Bennett et al [2016]
CNS = central nervous system

Skin. Non-scarring alopecia (with or without underlying fatty tissue) and subcutaneous fatty masses are the most typical skin anomalies.

- A smooth, hairless fatty tissue nevus of the scalp, the so-called nevus psiloliparus (NP) (Figure 1), is the dermatologic hallmark and found in about 75% of affected individuals.
  - In about 40%, fatty subcutaneous masses are seen in the frontotemporal or zygomatic region (Figure 2B, 2C, and Figure 7).
  - Rarely, subcutaneous lipomas are seen outside the craniofacial region.
- Alopecia without a fatty nevus can be linear or patchy, and may follow the lines of Blaschko (Figure 2A, 2B). Some affected individuals have scarring alopecia resulting from focal skin aplasia.
- Areas of focal skin aplasia are usually not extensive (up to a few cm in size) and there have been no reports of affected individuals requiring surgical treatment, such as skin graft, for focal skin aplasia.
- Small nodular skin tags (which histologically are fibromas, lipomas, fibrolipomas, or choristomas) are found in about 70%-75% of affected individuals, most often on the eyelids or following a line from the outer canthus to the tragus.
- Some individuals have several café au lait spots. Linear hyperpigmentation following the lines of Blaschko and (rarely) asymmetric growth may be seen [Moog et al 2007b].

Eyes. Choristomas, with or without other eye anomalies, are seen in the majority of affected individuals (Figure 2C). Several affected individuals have had irregular or disrupted eyebrows.

- Choristomas are benign ocular tumors and include epibulbar or limbal dermoids (dermolipomas) derived from epidermis and dermis, and lipodermoids, which consist mainly of fat and rarely decrease vision [Hunter 2006].

Dermolipomas can be associated with significant additional eye anomalies listed below.

- Most affected individuals without choristomas have one or more of the following associated eye anomalies:
  - Corneal and scleral anomalies
  - Other anterior chamber abnormalities
  - Ocular and palpebral colobomas
  - Aniridia
  - Microphthalmia
  - Calcification of the globe

Central nervous system (CNS) findings in 52 individuals who underwent imaging are summarized in Table 3. Note: The presence and extent of intracranial abnormalities does not correlate well with the severity of the developmental, skin, and eye findings.

- **Lipomas.** Intracranial lipomas (Figure 3) are the most common and specific CNS feature, found on neuroimaging in about 65% of affected individuals.
  - Almost 60% of these are located in the cerebello-pontine angle.
  - Spinal lipomas, which can extend over the whole length of the spinal cord (Figure 4), are also commonly seen on spinal cord imaging.

    Subcutaneous fatty masses may overlie the spinal lipomas or be found adjacent to the spinal cord (Figure 4).
- **Vascular abnormalities.** Abnormal intracranial blood vessels, such as leptomeningeal angiomatosis, thrombosed vascular malformations, and abnormal vessels, were found in nine individuals with ECCL in whom vascular imaging was performed.

  While this finding could represent ascertainment bias, it is suspected that these vascular abnormalities are common, as many of the other brain abnormalities observed could result from prenatal (or, less likely, postnatal) vascular perfusion defects or hemorrhage, including asymmetric brain atrophy, porencephaly, ventriculomegaly, and calcifications [Moog et al 2007a].

Table 3. Encephalocraniocutaneous Lipomatosis: Frequency of Central Nervous System Anomalies in 52 Affected Individuals Who Underwent Imaging

Intracranial Area/Feature	Type of Anomaly	Frequency [1]	Comment
Cerebral hemispheres	Any anomaly	43 (83%)	
	Ventriculomegaly	30 (57.7%)	Hydrocephalus in 9/30 (30%)
	Asymmetric atrophy	26 (50%)	
	Calcifications	24 (46.1%)	
	Arachnoid cysts	19 (36.5%)	
	Porencephaly	17 (32.7%)	
	Cortical dysplasia	15 (28.8%)	
	Callosal abnormalities	10 (19.2%)	Agenesis (partial or total) in 3/10 (30%); thin corpus callosum in 7/10 (70%)

Table 3. continued from previous page.

Intracranial Area/Feature	Type of Anomaly	Frequency [1]	Comment
Posterior fossa	Cerebellar hypoplasia	6 (11.5%)	Of those w/posterior fossa abnormalities, 6/6 (100%) had cerebellar hypoplasia; of the 6, 3 also had megacisterna magna.
Lipomas	Any lipoma	33 (63.5%)	Intracranial &/or spinal
	Intracranial lipomas	31 (59.6%)	In 18/31 (58%), lipomas were located in cerebello-pontine angle.
	Spinal lipomas	12/13 (92.3%) [2]	Not all persons underwent spinal MRI imaging.
Intracranial vessels	Abnormal or excessive vessels	5/9 (55%) [2]	
	Meningeal angiomatosis	6/9 (66%) [2]	

Adapted from Moog et al [2007a]

1. Unless otherwise specified, the denominator used for calculating the percentages is 52.

2. The numbers shown include only those individuals for whom information about the respective abnormality was available. Many others had no information available; thus, actual numbers and percentages are very likely higher.

Neurology. The spectrum of neurologic dysfunction is broad, ranging from normal cognitive development and no seizures to a very disabling disorder with severe intellectual disability (ID), intractable seizures, and other physical disabilities.

- Among reported individuals with ECCL, about one third have normal cognitive development, one third have mild developmental delay (DD) or ID, and the final one third have severe or unspecified DD/ID.
- About half of affected individuals had a history of typically infant- or childhood-onset epileptic seizures of different types that may be refractory or difficult to treat.

Musculoskeletal

- Jaw tumors identified as osteomas, odontomas, or ossifying fibromas have been described in affected individuals [Zielińska-Kaźmierska et al 2005, Moog 2009] (see **Tumors** below). These tumors are typically not malignant but can grow into the surrounding tissues, thus displacing teeth and other facial tissues.
- In severely affected individuals, possibly progressive, multiple lytic bone lesions affecting the long bones have been described (Figure 6) [Moog et al 2007b].

Tumors (cancers). Apart from lipomas and jaw tumors, ECCL is associated with increased risk for:

- Brain tumors, specifically low-grade gliomas (although high-grade gliomas have also been observed) [Phi et al 2010, Bennett et al 2016, Valera et al 2018].

  Pilocytic astrocytomas have been reported in six of 14 (43%) individuals with *FGFR1*-related ECCL; they have not been reported in those with *KRAS*-related ECCL (see Phenotype Correlations by Gene).

- Possibly Wilms tumor
  - The first reported child with ECCL and Wilms tumor also had severe growth restriction, which is unusual in individuals with ECCL, such that Wilms tumor in this situation could represent a rare co-occurrence with ECCL [Damar et al 2017].
  - Currently, insufficient evidence has accumulated to support a general recommendation for Wilms tumor screening in individuals with ECCL. Such screening may, however, be considered in individuals with *KRAS*-related ECCL in whom a pathogenic variant involving codon 12 is identified.

- Note: Wilms tumor and nephroblastomatosis have been reported in two individuals with postzygotic *KRAS* variants c.35G>A (p.Gly12Asp) and c.35G>T (p.Gly12Val), respectively, and phenotypes different from ECCL and oculoectodermal syndrome [Chang et al 2021] (see Genetically Related Disorders).

Other findings include:

- Macrocephaly (in ~20% of affected individuals);
- Congenital heart malformations, in particular aortic coarctation.

Oculoectodermal syndrome (OES; OMIM 600268) shares many features with ECCL, including focal alopecia or aplasia of the scalp, NP (possibly), periorbital skin tags, linear hyperpigmentation, ocular choristomas, macrocephaly, benign bone tumors, and coarctation of the aorta [Ardinger et al 2007]. Cranial MRI has been performed in about 60% of individuals with OES and may show arachnoid cysts, asymmetry of hemispheres, or mild dilatation of ventricles. Unlike ECCL, no lipomas or brain tumors (including pilocytic astrocytomas) have been reported in individuals with OES to date.

In at least seven individuals with a clinical diagnosis of OES, postzygotic activating variants in *KRAS* have been identified, many of which involve codon p.Ala146 [Boppudi et al 2016, McDonell et al 2018, Chacon-Camacho et al 2019]; pathogenic gain-of-function variants involving the p.Ala146 codon have also been identified in individuals who meet the clinical diagnostic criteria for ECCL. As noted above, recent data suggests that ECCL and OES are manifestations of a single spectrum (see Phenotype Correlations by Gene), as was first suggested in 2007 [Ardinger et al 2007, Moog et al 2007a]. Further research is needed to determine the phenotypes related to specific postzygotic activating pathogenic variants in *KRAS*.

Phenotype Correlations by Gene

Comparing *FGFR1*-related ECCL to *KRAS*-related ECCL, a gene-phenotype correlation emerges, especially when including individuals reported as having the OES phenotype who were found to have a *KRAS* pathogenic variant (see Nomenclature).

Compared to individuals with *FGFR1*-related ECCL, individuals with ***KRAS*-related ECCL** are:

- Less likely to have central nervous system lipomas
- Less likely to develop an astrocytoma (none reported to date)
- More likely to have:
  - Body asymmetry
  - Pigmentary mosaicism (hyperpigmented, hypopigmented, or both)
  - Epidermal nevi
  - Other malformations

Although these are preliminary considerations based on a small number of known affected individuals, the difference between *FGFR1*-related ECCL and *KRAS*-related ECCL (including those with an OES phenotype) needs to be reviewed in future, as different surveillance and management needs are likely – underscoring the need for molecular confirmation of the diagnosis.

Genotype-Phenotype Correlations

To date, all individuals with molecularly confirmed ECCL have had mosaicism for one of a few known gain-of-function pathogenic variants in either *FGFR1* or *KRAS* (see Molecular Genetics, Table 9, and Table 1).

Nomenclature

ECCL refers to the characteristic phenotypic findings involving the skin, eye, and central nervous system.

OES may be at one end of the ECCL spectrum [Ardinger et al 2007, Moog et al 2007a], and some individuals who do not fulfill the clinical diagnostic criteria for ECCL but display some features have been reported under this name. A subset of these individuals have indeed been found to have a mosaic *KRAS* pathogenic variant, providing further evidence that individuals with a clinical diagnosis of OES could fall within the spectrum of ECCL. However, pathogenic variants in other genes have also been found in individuals reported as having OES (see Differential Diagnosis).

Prevalence

The prevalence of ECCL is unknown. At least 85 individuals who meet the clinical diagnostic criteria or who have a molecular diagnosis of ECCL have been reported.

Genetically Related (Allelic) Disorders

Table 4 summarizes other phenotypes caused by pathogenic variants in *FGFR1*.

Table 4. *FGFR1* Allelic Disorders

Disorder	Molecular Mechanism
Hartsfield syndrome	Germline heterozygous or biallelic loss-of-function variants
Kallmann syndrome / Isolated GnRH deficiency	Germline loss-of-function variants
Osteoglophonic dysplasia (OMIM 166250)	Germline gain-of-function variants
Pfeiffer syndrome (See *FGFR* Craniosynostosis Syndromes Overview.)	Germline gain-of-function variants

GnRH = gonadotropin-releasing hormone

Table 5 summarizes other phenotypes caused by pathogenic variants in *KRAS*.

Table 5. *KRAS* Allelic Disorders

Disorder	Molecular Mechanism
Schimmelpenning-Feuerstein-Mims syndrome (also referred to as linear sebaceous nevus syndrome) (OMIM 163200) [1]	Postzygotic gain-of-function variants
Arteriovenous malformation of the brain; other vascular malformations (OMIM 108010)	Postzygotic gain-of-function variants
RAS-associated autoimmune leukoproliferative disorder (OMIM 614470)	Postzygotic gain-of-function variants
Cardiofaciocutaneous syndrome	Germline gain-of-function variants
Noonan syndrome	Germline gain-of-function variants

1. The c.35G>A (p.Gly12Asp) *KRAS* pathogenic variant has also been identified in an individual with a phenotype overlapping ECCL and Schimmelpenning-Feuerstein-Mims syndrome [Nagatsuma et al 2019] who meets the diagnostic criteria for ECCL noted in Establishing the Diagnosis.

Note: Wilms tumor and nephroblastomatosis have been reported in two individuals with postzygotic *KRAS* variants c.35G>A (p.Gly12Asp) and c.35G>T (p.Gly12Val), respectively, and phenotypes different from encephalocraniocutaneous lipomatosis (ECCL) and oculoectodermal syndrome [Chang et al 2021].

Sporadic tumors occurring as single tumors in the absence of other findings of ECCL frequently harbor somatic variants in *FGFR1* and/or *KRAS* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

The differential diagnosis of encephalocraniocutaneous lipomatosis (ECCL) also includes other mosaic RASopathies (a group of syndromes caused by mosaic mutations of the Ras/MAPK signaling pathway [Hafner & Groesser 2013]):

- ***NRAS.*** A postzygotic gain-of-function variant in *NRAS* (c.182A>G:p.Gln61Arg) was reported in a newborn with an oculoectodermal syndrome (OES) phenotype plus a few additional features such as dark brown to violet bullae over the scalp and unilateral polymicrogyria [Richters et al 2020].
- **Neurocutaneous melanosis** (NCMS) (OMIM 249400) is a severe form of congenital melanocytic nevus syndrome (CMNS) (OMIM 137550) in association with abnormalities of the central nervous system possibly leading to seizures and other neurologic signs. In rare cases, NCMS may present with the skin, eye, or brain findings seen in OES or ECCL [Ahmed et al 2002, Jain et al 2014]. NCMS is caused by postzygotic activating variants in *NRAS*. The individual mentioned above with a postzygotic variant in *NRAS* and an OES phenotype showed a dark coloration of bullous scalp lesions but no further signs of CMNS [Richters et al 2020].
- **Schimmelpenning-Feuerstein-Mims syndrome** (SFMS, also referred to as linear sebaceous nevus syndrome and, formerly, epidermal nevus syndrome) (OMIM 163200). The dermatologic hallmark of this disorder is sebaceous nevi and other epidermal nevi following the lines of Blaschko, which are rarely seen in ECCL. SFMS is associated with congenital anomalies of the eye, brain, and skeleton, which overlap with features seen in ECCL (choristomas, coloboma, hemimegalencephaly, cortical malformations, cortical atrophy, porencephalic cysts, calcifications, lipoma [rarely], and focal bone lesions) [Wang et al 2014]. SFMS (as well as isolated sebaceous nevus) has been shown to result from postzygotic activating variants in *HRAS*, *KRAS*, or *NRAS* [Groesser et al 2012, Aslam et al 2014]. One individual with the postzygotic activating *KRAS* variant c.35G>A (p.Gly12Asp) has been reported with a phenotype that overlaps SFMS and ECCL [Nagatsuma et al 2019].

Oculocerebrocutaneous syndrome (OCCS) (OMIM 164180). Like ECCL, OCCS presents with focal skin lesions and congenital anomalies of the eyes and the brain. OCCS is characterized by hypo- or aplastic skin defects and nodular or pedunculated skin tags, cystic microphthalmia, a combination of forebrain anomalies, and a specific mid-hindbrain malformation [Moog & Dobyns 2018]. The skin anomalies primarily affect the region of the head and the neck. OCCS is hypothesized to be a mosaic disorder, but the specific cause has not yet been identified.

Management

No clinical practice guidelines for encephalocraniocutaneous lipomatosis (ECCL) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ECCL, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Encephalocraniocutaneous Lipomatosis

System/Concern	Evaluation	Comment
Skin	Full skin exam	For evidence of nevus psiloliparus, subcutaneous fatty lipomas, cutis aplasia, alopecia, & pigmentary anomalies
Eye	Ophthalmologic exam	Assess for evidence of choristoma, or any other eye anomaly.

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
CNS	Neurologic exam	
	Brain & spinal MRI/MRA	To evaluate for intracranial & spinal lipomas, tumors, malformations, &/or vascular anomalies
	Consider EEG.	If seizures are a concern
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Musculoskeletal	Consider a skeletal survey.	To assess for osteomas, ossifiying fibromas, & lytic bone lesions
Dental involvement	Exam by pediatric or adult dentist, depending on age	• Assess for odontomas. • Further imaging of jaw for jaw tumors may be considered.
Genitourinary	Consider baseline renal ultrasound in persons up to age 8 yrs.	Only in those who have a *KRAS* pathogenic variant that involves codon 12
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of ECCL to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CNS =- central nervous system; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 7. Treatment of Manifestations in Individuals with Encephalocraniocutaneous Lipomatosis

Manifestation/Concern	Treatment	Considerations/Other
NP, alopecia, focal skin aplasia/hypoplasia, nodular skin tags	Standard treatment per dermatologist	Many skin findings do not require active mgmt.
Choristomas / Eye anomalies	Standard treatment per ophthalmologist	Community vision services through early intervention or school district for those w/significant visual impairment
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Low-grade gliomas	Standard treatment per oncologist/neuro-oncologist	1 person w/*FGFR1*-related ECCL & a progressive pilocytic astrocytoma was treated w/trametinib (a MEK inhibitor) w/resultant stable tumor size after 6 mos of treatment. [2]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Lytic bone lesions	Standard treatment per orthopedist, if needed	

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Jaw tumors	Standard treatment per dentist	Such tumors are not typically malignant but can grow into surrounding tissues.
Wilms tumor	Standard treatment per oncologist	• It is currently unclear if persons w/ECCL are at ↑ risk for development of Wilms tumor. • See also Wilms Tumor Predisposition.
Family support & resources	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; NP = nevus psiloliparus
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Bavle et al [2018]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Surveillance

Table 8. Recommended Surveillance for Individuals with Encephalocraniocutaneous Lipomatosis

System/Concern	Evaluation	Frequency
Neurologic	Consider brain MRI to screen for brain tumors. [1]	Typically annually, [2] or as clinically indicated
	Monitor those w/seizures as clinically indicated.	At each visit
	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Development	Monitor developmental progress & educational needs.	
Eye	Ophthalmologic eval	Annually in childhood & adolescence or as clinically indicated
Dental	Dental eval	At least every 6 mos
Genitourinary	Renal ultrasound	Consider every 3 mos until age 8 yrs in those w/a KRAS pathogenic variant involving codon 12. [3]

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources) & care coordination.	At each visit

1. Brain tumors have not been reported in individuals with *KRAS*-related ECCL.
2. Unless the affected individuals have molecularly confirmed *KRAS*-related ECCL, in which case brain MRI should be performed based on clinical signs and symptoms.
3. There is insufficient evidence to support a general recommendation for Wilms tumor screening in individuals with ECCL, but such screening may be considered in those with a *KRAS* pathogenic variant that involves codon 12.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Encephalocraniocutaneous lipomatosis (ECCL) is not known to be inherited. No confirmed vertical transmission or sib recurrence has been reported.

Risk to Family Members

Parents of a proband. No parent of a child with ECCL has had any significant, distinctive manifestations of the disorder, nor would such a finding be expected, given the postzygotic mutational mechanism of this disorder.

Sibs of a proband. Given the postzygotic mutational mechanism of ECCL, the risk for an affected sib would be expected to be the same as in the general population.

Offspring of a proband. Reproductive outcome data on adults with ECCL are limited. There are no instances of vertical transmission of ECCL.

Other family members. The risk to other family members is presumed to be the same as in the general population.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mosaic pathogenic variant. This is a relatively new area for clinical genetics, as only a small (albeit growing) number of disorders are known to be caused by this genetic mechanism. Counseling for recurrence risks in ECCL should emphasize that, while no pregnancy is at zero risk,

all evidence suggests that the risk of recurrence for this disorder is not increased compared to the general population.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). Because ECCL is a mosaic disorder, DNA derived from affected tissue should be banked in addition to DNA derived from lymphocytes.

Prenatal Testing and Preimplantation Genetic Testing

As ECCL is not known to be inherited, prenatal diagnosis is usually not indicated. The authors recognize no potential role for preimplantation genetic testing in ECCL.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Born a Hero**
  www.bornahero.org
- **MedlinePlus**
  Encephalocraniocutaneous lipomatosis

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Encephalocraniocutaneous Lipomatosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGFR1	8p11.23	Fibroblast growth factor receptor 1	FGFR1 database	FGFR1	FGFR1
KRAS	12p12.1	GTPase KRas	KRAS database NSEuroNet database - KRAS	KRAS	KRAS

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Encephalocraniocutaneous Lipomatosis (View All in OMIM)

136350	FIBROBLAST GROWTH FACTOR RECEPTOR 1; FGFR1

Table B. continued from previous page.

190070	KRAS PROTOONCOGENE, GTPase; KRAS
613001	ENCEPHALOCRANIOCUTANEOUS LIPOMATOSIS; ECCL

Molecular Pathogenesis

FGFR1 encodes a growth factor receptor, which, when activated, signals through the RAS/mitogen activated protein kinase (MAPK) pathway. *KRAS* is a component of the RAS/MAPK pathway, critical for regulating the pathway's activity level. Cell growth and cell differentiation are affected by this signaling pathway. Dysregulation of this signaling pathway during embryogenesis or later in life results in developmental malformations or malignant tumors, respectively. The pathogenic variants reported in ECCL are of postzygotic origin, but arise early during development. Dysregulation of the RAS/MAPK pathway - typically, increased activation - results in characteristic developmental malformations reflecting the mosaic distribution of the pathogenic variant. The spectrum of pathogenic missense variants causing developmental malformations but remaining compatible with survival is likely narrow - accounting for the limited number of pathogenic variants identified in ECCL.

Mechanism of disease causation. Gain of function

Note: It is currently unknown why different gain-of-function pathogenic variants cause different, completely nonoverlapping phenotypes (e.g., *FGFR1* p.Asn547Lys substitutions are associated with ECCL, but *FGFR1* p.Pro252Arg substitutions cause Pfeiffer syndrome, a craniosynostosis syndrome).

Gene-specific laboratory technical considerations. In affected tissues, any sequencing method may detect ECCL-specific pathogenic variants. However, in unaffected tissues (blood, saliva, normal-appearing skin) and possibly also in affected tissues, low levels of mosaicism for the ECCL-specific pathogenic variants in *FGFR1* and *KRAS* can only be detected using targeted approaches that yield deep sequencing data. The authors therefore recommend use of deep targeted approaches, particularly deep amplicon-based next-generation sequencing or digital droplet PCR (ddPCR) when ECCL is suspected.

Table 9. Encephalocraniocutaneous Lipomatosis: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Reference
FGFR1	NM_023110.2 NP_075598.2	c.1638C>A	p.Asn546Lys	Bennett et al [2016]
		c.1966A>G	p.Lys656Glu	
KRAS	NM_004985.5 NP_004976.2	c.35G>A	p.Gly12Asp	Nagatsuma et al [2019]
		c.38G>A	p.Gly13Asp	Peacock et al [2015]
		c.57G>C	p.Leu19Phe	
		c.436G>A	p.Ala146Thr	Boppudi et al [2016], McDonell et al [2018], Chacon-Camacho et al [2019]
		c.437C>T	p.Ala146Val	Boppudi et al [2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 are in alphabetic order.

Cancer and Benign Tumors

FGFR1 and *KRAS* are well known proto-oncogenes with somatic pathogenic *KRAS* variants comprising the most common genetic abnormalities in cancer, particularly pancreatic, colon, and lung cancers [Jancík et al 2010, Hunter et al 2015]. However, cancer has not been reported in *KRAS*-related ECCL.

Somatic *FGFR1* pathogenic variants have also been observed in many different cancer types, including squamous cell (lung, head and neck, esophagus) carcinoma, ovarian cancers, and osteosarcoma [Dienstmann et al 2014]. More relevant for ECCL, somatic pathogenic variants in *FGFR1* are common in pilocytic astrocytomas and related midline gliomas [Jones et al 2013, Picca et al 2018], the most frequent cancer reported in individuals with ECCL.

Finally, somatic pathogenic variants in both *KRAS* (the same as ECCL) and *FGFR1* (different from ECCL) have been described in giant cell lesions of the jaw, which can occur in individuals with ECCL [Gomes et al 2018].

Chapter Notes

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References

Literature Cited

Ahmed I, Tope WD, Young TL, Miller DM, Bloom KE. Neurocutaneous melanosis in association with encephalocraniocutaneous lipomatosis. J Am Acad Dermatol. 2002;47:S196–200. PubMed PMID: 12140461.

Ardinger HH, Horii KA, Begleiter ML. Expanding the phenotype of oculoectodermal syndrome: possible relationship to encephalocraniocutaneous lipomatosis. Am J Med Genet A. 2007;143A:2959–62. PubMed PMID: 17963257.

Aslam A, Salam A, Griffiths CEM, McGrath JA. Naevus sebaceus: a mosaic RASopathy. Clin Exp Dermatol. 2014;39:1–6. PubMed PMID: 24341474.

Bavle A, Shah R, Gross N, Gavula T, Ruiz-Elizalde A, Wierenga K, McNall-Knapp R. Encephalocraniocutaneous lipomatosis. J Pediatr Hematol Oncol. 2018;40:553–4. PubMed PMID: 29683947.

Bennett JT, Tan TY, Alcantara D, Tétrault M, Timms AE, Jensen D, Collins S, Nowaczyk MJM, Lindhurst MJ, Christensen KM, Braddock SR, Brandling-Bennett H, Hennekam RCM, Chung B, Lehman A, Su J, Ng S, Amor DJ, Majewski J, Biesecker LG, Boycott KM, Dobyns WB, O'Driscoll M, Moog U, McDonell LM, et al. Mosaic activating mutations in FGFR1 cause encephalocraniocutaneous lipomatosis. Am J Hum Genet. 2016;98:579–87. PubMed PMID: 26942290.

Boppudi S, Bögershausen N, Hove HB, Percin EF, Aslan D, Dvorsky R, Kayhan G, Li Y, Cursiefen C, Tantcheva-Poor I, Toft PB, Bartsch O, Lissewski C, Wieland I, Jakubiczka S, Wollnik B, Ahmadian MR, Heindl LM, Zenker M. Specific mosaic KRAS mutations affecting codon 146 cause oculoectodermal syndrome and encephalocraniocutaneous lipomatosis. Clin Genet. 2016;90:334–42. PubMed PMID: 26970110.

Chacon-Camacho OF, Lopez-Moreno D, Morales-Sanchez MA, Hofmann E, Pacheco-Quito M, Wieland I, Cortes-Gonzalez V, Villanueva-Mendoza C, Zenker M, Zenteno JC. Expansion of the phenotypic spectrum and description of molecular findings in a cohort of patients with oculocutaneous mosaic RASopathies. Mol Genet Genomic Med. 2019;7:e625. PubMed PMID: 30891959.

Chang CA, Perrier R, Kurek KC, Estrada-Veras J, Lehman A, Yip S, Hendson G, Diamond C, Pinchot JW, Tran JM, Arkin LM, Drolet BA, Napier MP, O'Neill SA, Balci TB, Keppler-Noreuil KM. Novel findings and expansion of phenotype in a mosaic RASopathy caused by somatic KRAS variants. Am J Med Genet A. 2021;185:2829–45. PubMed PMID: 34056834.

Córdoba A, Graue-Hernández EO, Navas A, Chacon-Camacho OF, Zenteno JC, Ramirez-Miranda A, Bermudez-Magner JA, Ordaz-Robles T, Pérez-Solórzano S, Olivo-Payne A. Giant ocular lipodermoid cyst in encephalocraniocutaneous lipomatosis: surgical treatment and genetic analysis. Am J Case Rep. 2019;20:1566–71. PubMed PMID: 31649234.

Damar Ç, Yaman A, Ali İkidağ M, Pekpak E, Olgaç A. Encephalocraniocutaneous lipomatosis with Wilms' tumor. Pediatr Int. 2017;59:835–6. PubMed PMID: 28612492.

Dienstmann R, Rodon J, Prat A, Perez-Garcia J, Adamo B, Felip E, Cortes J, Iafrate AJ, Nuciforo P, Tabernero J. Genomic aberrations in the FGFR pathway: opportunities for targeted therapies in solid tumors. Ann Oncol. 2014;25:552–63. PubMed PMID: 24265351.

Gomes CC, Gayden T, Bajic A, Harraz OF, Pratt J, Nikbakht H, Bareke E, Diniz MG, Castro WH, St-Onge P, Sinnett D, Han H, Rivera B, Mikael LG, De Jay N, Kleinman CL, Valera ET, Bassenden AV, Berghuis AM, Majewski J, Nelson MT, Gomez RS, Jabado N. TRPV4 and KRAS and FGFR1 gain-of-abnormal-function mutations drive giant cell lesions of the jaw. Nat Commun. 2018;9:4572. PubMed PMID: 30385747.

Groesser L, Herschberger E, Ruetten A, Ruivenkamp C, Lopriore E, Zutt M, Langmann T, Singer S, Klingseisen L, Schneider-Brachert W, Toll A, Real FX, Landthaler M, Hafner C. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. Nat Genet. 2012;44:783–7. PubMed PMID: 22683711.

Hafner C, Groesser L. Mosaic RASopathies. Cell Cycle. 2013;12:43–50. PubMed PMID: 23255105.

Hunter AG. Oculocerebrocutaneous and encephalocraniocutaneous lipomatosis syndromes: blind men and an elephant or separate syndromes? Am J Med Genet A. 2006;140:709–26. PubMed PMID: 16523517.

Hunter JC, Manandhar A, Carrasco MA, Gurbani D, Gondi S, Westover KD. Biochemical and structural analysis of common cancer-associated KRAS mutations. Mol Cancer Res. 2015;13:1325–35. PubMed PMID: 26037647.

Jain P, Chakrabarty B, Kumar A, Gupta N, Kabra M, Gulati S. Encephalocraniocutaneous lipomatosis with neurocutaneous melanosis. J Child Neurol. 2014;29:846–9. PubMed PMID: 23620525.

Jancík S, Drábek J, Radzioch D, Hajdúch M. Clinical relevance of KRAS in human cancers. J Biomed Biotechnol. 2010;2010:150960. PubMed PMID: 20617134.

Jones DT, Hutter B, Jäger N, Korshunov A, Kool M, Warnatz HJ, Zichner T, Lambert SR, Ryzhova M, Quang DA, Fontebasso AM, Stütz AM, Hutter S, Zuckermann M, Sturm D, Gronych J, Lasitschka B, Schmidt S, Seker-Cin H, Witt H, Sultan M, Ralser M, Northcott PA, Hovestadt V, Bender S, Pfaff E, Stark S, Faury D, Schwartzentruber J, Majewski J, Weber UD, Zapatka M, Raeder B, Schlesner M, Worth CL, Bartholomae CC, von Kalle C, Imbusch CD, Radomski S, Lawerenz C, van Sluis P, Koster J, Volckmann R, Versteeg R, Lehrach H, Monoranu C, Winkler B, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, Ebinger M, Schuhmann MU, Cho YJ, Pomeroy SL, von Deimling A, Witt O, Taylor MD, Wolf S, Karajannis MA, Eberhart CG, Scheurlen W, Hasselblatt M, Ligon KL, Kieran MW, Korbel JO, Yaspo ML, Brors B, Felsberg J, Reifenberger G, Collins VP, Jabado N, Eils R, Lichter P, Pfister SM, et al. Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet. 2013;45:927–32. PubMed PMID: 23817572.

Kordacka J, Zakrzewski K, Gruszka R, Witusik-Perkowska M, Taha J, Sikorska B, Liberski PP, Zakrzewska M. Sensitive detection of FGFR1 N546K mosaic mutation in patient with encephalocraniocutaneous lipomatosis and pilocytic astrocytoma. Am J Med Genet A. 2019;179:1622–7. PubMed PMID: 31173478.

McDonell LM, Leung GK, Daoud H, Ip J, Chim S, Luk HM, Lan L, Boycott KM, Chung BH, et al. Mosaic KRAS mutation in a patient with encephalocraniocutaneous lipomatosis and renovascular hypertension. Am J Med Genet A. 2018;176:2523–7. PubMed PMID: 30289595.

Moog U. Encephalocraniocutaneous lipomatosis. J Med Genet. 2009;46:721–9. PubMed PMID: 19574261.

Moog U, Dobyns WB. An update on oculocerebrocutaneous (Delleman-Oorthuys) syndrome. Am J Med Genet C Semin Med Genet. 2018;178:414–22. PubMed PMID: 30580480.

Moog U, Jones MC, Viskochil DH, Verloes A, Van Allen MI, Dobyns WB. Brain anomalies in encephalocraniocutaneous lipomatosis. Am J Med Genet A. 2007a;143A:2963–72. PubMed PMID: 18000987.

Moog U, Roelens F, Mortier GR, Sijstermans H, Kelly M, Cox GF, Robson CD, Kimonis VE. Encephalocraniocutaneous lipomatosis accompanied by the formation of bone cysts: harboring clues to pathogenesis? Am J Med Genet A. 2007b;143A:2973–80. PubMed PMID: 18000896.

Nagatsuma M, Takasawa K, Yamauchi T, Nakagawa R, Mizuno T, Tanaka E, Yamamoto K, Uemura N, Kashimada K, Morio T. A postzygotic KRAS mutation in a patient with Schimmelpenning syndrome presenting with lipomatosis, renovascular hypertension, and diabetes mellitus. J Hum Genet. 2019;64:177–81. PubMed PMID: 30443000.

Peacock JD, Dykema KJ, Toriello HV, Mooney MR, Scholten DJ 2nd, Winn ME, Borgman A, Duesbery NS, Hiemenga JA, Liu C, Campbell S, Nickoloff BP, Williams BO, Steensma M. Oculoectodermal syndrome is a mosaic RASopathy associated with KRAS alterations. Am J Med Genet A. 2015;167:1429–35. PubMed PMID: 25808193.

Phi JH, Park SH, Chae JH, Wang KC, Cho BK, Kim SK. Papillary glioneuronal tumor present in a patient with encephalocraniocutaneous lipomatosis: case report. Neurosurgery. 2010;67:E1165–9. PubMed PMID: 20881536.

Picca A, Berzero G, Bielle F, Touat M, Savatovsky J, Polivka M, Trisolini E, Meunier S, Schmitt Y, Idbaih A, Hoang-Xuan K, Delattre JY, Mokhtari K, Di Stefano AL, Sanson M. FGFR1 actionable mutations, molecular specificities, and outcome of adult midline gliomas. Neurology. 2018;90:e2086–e2094. PubMed PMID: 29728520.

Richters RJH, Seyger MMB, Meeuwis KAP, Rinne T, Eijkelenboom A, Willemsen MA. Oculoectodermal syndrome - encephalocraniocutaneous lipomatosis associated with NRAS mutation. Acta Derm Venereol. 2020;100:adv00103. PubMed PMID: 31633190.

Valera ET, McConechy MK, Gayden T, Rivera B, Jones DTW, Wittmann A, Han H, Bareke E, Nikbakht H, Mikael L, Queiroz RG, Suazo VK, Phi JH, Kim SK, Park SH, Fukaya R, Yum MS, Ko TS, de Oliveira RS, Machado HR, Brassesco MS, do Santos AC, Simão GN, Ramalho LNZ, Neder L, Scrideli CA, Tone LG, Majewski J, Jabado N. Methylome analysis and whole-exome sequencing reveal that brain tumors associated with encephalocraniocutaneous lipomatosis are midline pilocytic astrocytomas. Acta Neuropathol. 2018;136:657–60. PubMed PMID: 30143858.

Wang SM, Hsieh YJ, Chang KM, Tsai HL, Chen CP. Schimmelpenning syndrome: a case report and literature review. Pediatr Neonatol. 2014;55:487–90. PubMed PMID: 23597534.

Zielińska-Kaźmierska B, Grodecka J, Jabłońska-Polakowska L, Arkuszewski P. Mandibular osteoma in the encephalocraniocutaneous lipomatosis. J Craniomaxillofac Surg. 2005;33:286–9. PubMed PMID: 15975807.

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