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# 5q14.3 Neurocutaneous Syndrome: A Novel Continguous Gene Syndrome Caused by Simultaneous Deletion of *RASA1* and *MEF2C*

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**Haploinsufficiency of *RASA1*, located on chromosome 5q14.3, has been identified as the etiology underlying the disorder capillary malformation–arteriovenous malformation (CM–AVM). Recently, haploinsufficiency of *MEF2C*, located 1.33 Mb distal to *RASA1* on chromosome 5q14.3, has been implicated as the genetic etiology underlying a complex array of deficits including mental retardation, hypotonia, absent speech, seizures, and brain anomalies. Here we report a patient who is haploinsufficient in both *RASA1* and *MEF2C* who presents with dermatologic and neurologic abnormalities that constitute a 5q14.3 neurocutaneous syndrome. This finding highlights the need to assess for CM–AVM in patients with neurologic features consistent with *MEF2C* haploinsufficiency, and vice versa.**



**Key words:** neurocutaneous syndromes; RASA; MEF2C; CM–AVM; mental retardation

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## INTRODUCTION

*RASA1*, a gene on the long arm of chromosome 5, encodes p120-RasGTPase-activating-protein, a negative regulator of the Ras/MAPK-signaling pathway [Clark et al., 1993]. In 2003, Eerola et al. reported six families with mutations of one copy of *RASA1* who exhibited atypical capillary malformations (CMs) and some arteriovenous malformations (AVMs) or fistulas (AVFs). Hence, this entity was named CM–AVM disorder [Eerola et al., 2003]. CMs consist of capillaries and venules in the reticular dermis that may be dilated, increased in number, or both. Clinically, CM–AVM patients exhibit multiple pink-red, round, or oval CMs that have been reported up to 15 cm in size [Hershkovitz et al., 2008; Revencu et al., 2008]. These patients' AVMs and AVFs are typically located in the head and neck region [Boon et al., 2005], although localization of these vascular anomalies entirely within the spine is possible [Thiex et al., 2010]. Due to variable expressivity and incomplete penetrance, paradominant inheritance has been proposed but remains unproven [Limaye et al., 2009].

Over the last 2 years, interstitial deletions within chromosome region 5q14.3q15 have been associated with a spectrum of findings that includes developmental delay/mental retardation, hypotonia, absent speech, mild facial dysmorphism, seizures, and brain anomalies. While there has been variation in facial dysmorphism, some of the more commonly reported characteristics include frontal bossing, up- or down-slanting palpebral fissures, short philtrum, open-mouth gaze, and micrognathia. This phenotype has been described in six reports encompassing 19 patients with a 5q14.3q15 microdeletion (Fig. 1) [Cardoso et al., 2009; Engels et al., 2009; Le Meur et al., 2010; Novara et al., 2010; Nowakowska et al., 2010; Zweier et al., 2010]. An emerging consensus points to haploinsufficiency of *MEF2C*, a member of the myocyte enhancer factor-2 (MEF2) transcription factor family [Potthoff et al., 2007], as the genetic etiology underlying this complex phenotype. This consensus was built upon much thoughtful research, as the aforementioned

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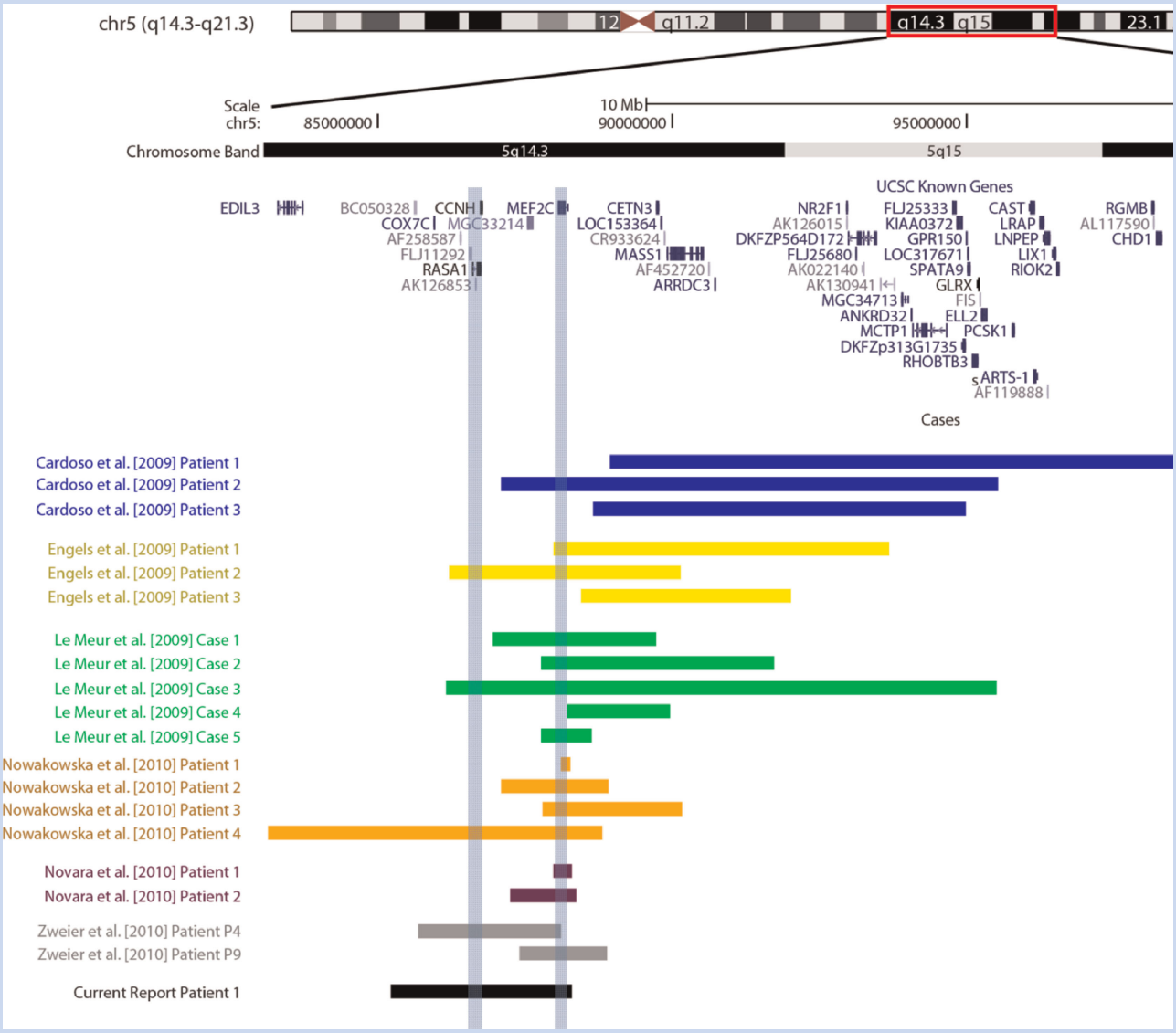


**FIG. 1. Ideogram depicting the locations of reported 5q14.3q15 microdeletions. [Color figure can be seen in the online version of this article, available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833]**

19 patients did not all share a commonly deleted gene. Indeed, 3 of the 19 patients lack deletion of *MEF2C*, as seen in Figure 1, so *MEF2C*'s role in the 5q14.3q15 microdeletion phenotype was not self-evident. *MEF2C*'s causative role was buttressed with the identification of two affected patients whose microdeletions only involved *MEF2C* [Novara et al., 2010; Nowakowska et al., 2010] and another patient who had a nonsense mutation of *MEF2C* in lieu of a 5q14.3q15 deletion [Le Meur et al., 2010].

Here we report on a patient with a 5q14.3 deletion who presented with both CM–AVM and the neurologic and dysmorphic findings recently associated with *MEF2C* haploinsufficiency. This patient's phenotype of dermatologic and neurologic abnormalities constitutes a 5q14.3 neurocutaneous syndrome due to the contiguous deletion of *RASA1* and *MEF2C*. An analysis of previous 5q14.3q15 microdeletion reports reveals that other patients may have manifested this neurocutaneous syndrome, but the significance of dermatologic findings was not always appreciated.

## PATIENT REPORT

The propositus, a Caucasian male, was born to a nonconsanguinous 26-year-old G6P1 mother and 31-year-old father at 39 weeks gestation. The mother reported decreased fetal movement in the last trimester. The prenatal course was otherwise uncomplicated, and the propositus arrived with Apgar scores of 9 and 10. At birth, the patient weighed 2.9 kg (15th centile) and measured 49.5 cm (43rd centile), with a head circumference of 33 cm (9th centile). The patient's family history included no birth defects, mental retardation, nor other inherited diseases. Both parents have normal karyotypes.

## Dermatologic Findings

At birth, no lesions were observed on the patient's skin; by 3 years of age, the patient's skin exhibited multiple lesions. On his trunk, extremities, and head, the patient had 17 pink-red, non-pruritic, flat, and round lesions consistent with CMs. The center of each lesion contained telangiectatic vessels that blanched with pressure. Dermatopathologic evaluation revealed slightly dilated, thin-walled vascular spaces in the dermis. Other findings included a reddish-tan, atrophic patch with a diameter of 1.5 cm just inferior to the suprasternal notch. The patient had two large, irregularly shaped CMs, one in the left popliteal fossa measuring 2.5 cm at its greatest length, and one on the upper left posterior thigh measuring 5 cm.

In adolescence, the patient's dermatologic abnormalities persisted. At age 16, physical examination revealed 115 round and oval CMs measuring 0.5–2.0 cm on the patient's trunk, extremities, and head. Many of these lesions featured a white halo that encircled a pink-red center. Doppler ultrasound of five CMs with halos detected no fast blood flow. The reddish-tan patch near the patient's suprasternal notch was still present (Fig. 2a); telangiectasias were visible within this lesion. The CMs in the left popliteal fossa (Fig. 2b)

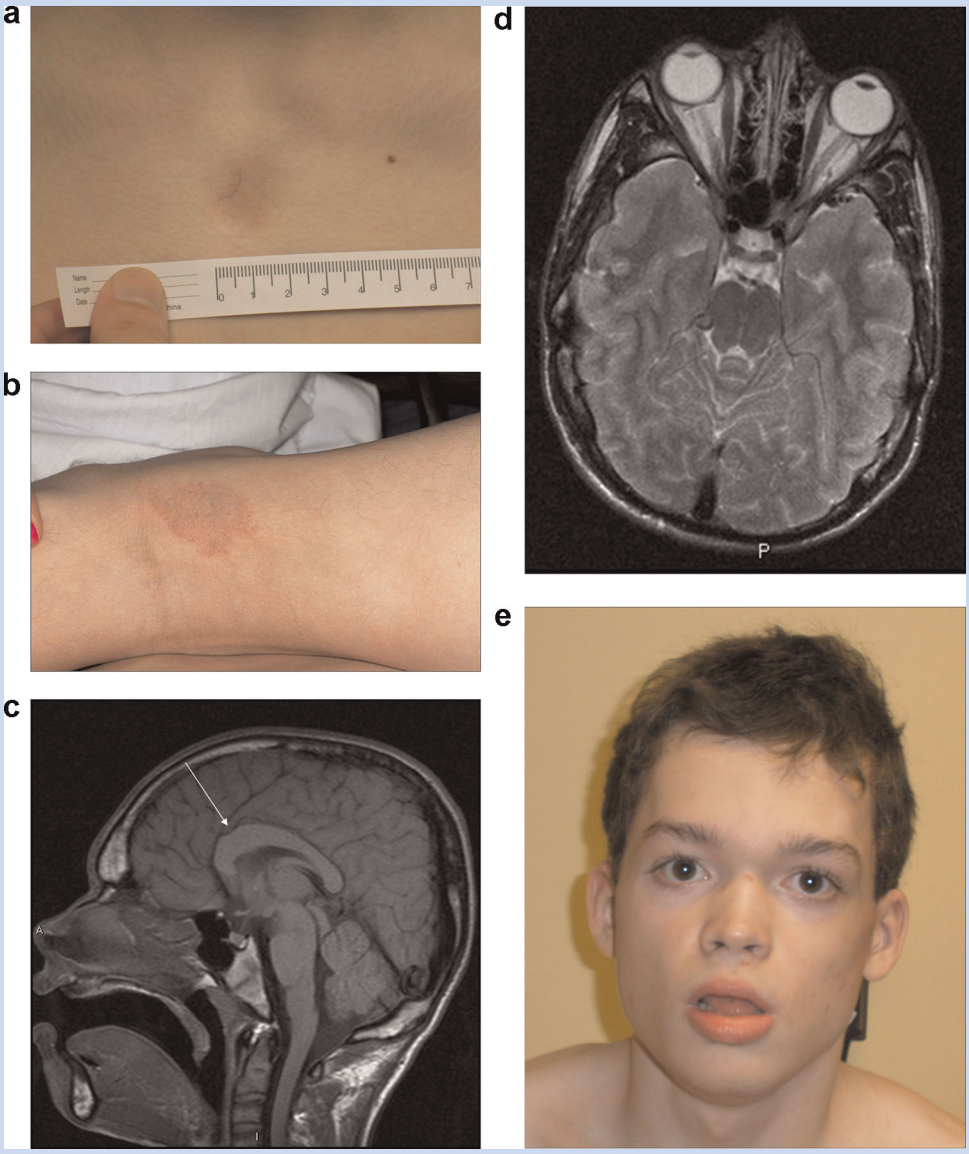


FIG. 2. a: Atrophic patch immediately inferior to the suprasternal notch. Close inspection reveals telangiectasias. b: Large, irregularly shaped capillary malformation in the patient's left popliteal fossa. c: Cranial MRI at 16 years of age reveals an abnormally thickened anterior corpus callosum, as indicated by the arrow. d: Cranial MRI at 16 years of age reveals a simplified gyral pattern with gyral thickening in the temporal lobes. e: The patient exhibits the characteristic open-mouth gaze. [Color figure can be seen in the online version of this article, available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833]

and on the upper left posterior thigh had grown larger (4 and 10 cm in greatest length, respectively). Periorbitally and on the patient's right elbow and knee, the patient had areas of hypopigmentation consistent with vitiligo. The onset of these vitiliginous changes was at age 13.

### Neurologic Findings

Motor delay and hypotonia of the shoulder girdle became evident at 6 months of age. At 10 months, the patient showed 2+ reflexes and marked axial hypotonia. At that age, formal testing confirmed significant developmental delay; visual or auditory deficits could not be found. The patient could not sit unsupported until age 2.5 years. In early childhood, the patient began to exhibit stereotypic movements in the form of hand flapping and persistent bruxism. He experienced two myoclonic seizures, but electroencephalograms at ages 6 and 15 months detected no seizure activity.

The patient underwent cranial magnetic resonance imaging at the ages of 6 months, 33 months, and 16 years. MRI found the corpus callosum to be abnormally thick anteriorly in the body and genu (Fig. 2c). In the temporal lobes, the gyral pattern was simplified and the gyri were abnormally thickened (Fig. 2d). No periventricular heterotopia was present. At 33 months of age, MRI showed a delay in myelination that was no longer present at 16 years of age. Magnetic resonance angiography found no vascular malformations in the head or neck. No imaging of the spine is available.

At 14 years of age, the patient was severely mentally retarded, had never walked, and had no speech, though he sporadically uttered noises. He had never shown regression. Neurologic examination revealed global hypotonia, and reflexes were 3+ throughout his body. No cranial nerve deficit was found.

### Other Findings

On examination at 10 months, the patient had a prominent forehead with bitemporal narrowing and hypoplastic orbital ridges. The palpebral fissures were downslanting, and medial eyebrows were sparse bilaterally. Nostrils were hypoplastic, and his nose was short and upturned. At 14 years of age, the patient's appearance remained dysmorphic, though his nose now appeared normal (Fig. 2e). At that age the patient weighed 49.5 kg (43rd centile) with a head circumference of 58 cm (98th centile).

A karyotype with a band resolution of 550 was normal. Subtelomeric probe analysis, fragile X testing, *ARX* sequencing, *MECP2* sequencing, and uniparental disomy studies of chromosome 15 were unremarkable. Levels of plasma amino acids, carnitine, and CPK were within normal limits.

## MOLECULAR CYTOGENETIC ANALYSIS

Whole-genome cytogenetic array comparative genomic hybridization (aCGH) analysis was carried out using a custom-designed 44K oligonucleotide array with a backbone resolution of ~250 kb [Baldwin et al., 2008]. A ~3.1 Mb interstitial deletion of 5q14.3 was identified spanning from 85,208,054 to 88,290,255 bp (hg17 assembly). This microdeletion encompassed five known genes: *COX7C*, *RASA1*, *CCNH*, *TMEM161B*, and *MEF2C*. FISH analysis confirmed the deletion; FISH analyses of the parents found the deletion to be de novo. Additionally, a smaller ~0.5 Mb interstitial deletion of Chr17q21.31 was observed. This deletion is a known variant that does not cause clinical abnormalities [Iafrate et al., 2004]. No other copy number abnormalities were found on the 44K oligonucleotide array.

## DISCUSSION

### MEF2C

We have reported a patient with a ~3.1 Mb microdeletion of 5q14.3 that encompasses five known genes. Since 2009, six authors have reported on 5q14.3q15 microdeletions and the associated clinical findings [Cardoso et al., 2009; Engels et al., 2009; Le Meur et al., 2010; Nowakowska et al., 2010; Novara et al., 2010; Zweier et al., 2010]. From these reports, a common syndrome of developmental delay/mental retardation, hypotonia, absent speech, mild facial dysmorphology, seizures, and brain anomalies emerges. An emerging consensus attributes these deficits to *MEF2C* haploinsufficiency. The patient reported herein shares the *MEF2C* haploinsufficiency phenotype that has appeared in these recent reports.

### RASA1

The patient reported here presented with classic characteristics of CM–AVM, including multiple atypical CMs. Previously reported cases of CM–AVM were shown to be caused by mutations of the *RASA1* gene [Eerola et al., 2003; Hershkovitz et al., 2008; Revencu et al., 2008]. In contrast, this patient's *RASA1* haploinsufficiency was due to a deletion of the entire *RASA1* gene. Thirty-three percent of *RASA1* haploinsufficient patients have fast-flow vascular anomalies, of which slightly less than half are located in the head and neck region [Revencu et al., 2008]. Early identification and treatment (when possible) of such anomalies may attenuate patients' neurologic deficits. Magnetic resonance imaging of our patient's head and neck revealed no AVMs or AVFs.

Many of our patient's CMs featured white halos surrounding the central telangiectasia. Boon et al. [2005] suggested that such halos may be due to vascular steal from an underlying AVM. While Doppler ultrasound has identified increased flow in some RASA1-deficient patients [Boon et al., 2005], this could not be detected in our patient's lesions, perhaps because the Doppler is not sensitive enough. Our patient also presented with vitiligo around his eyes and on his right elbow and knee. Vitiligo has not previously been associated with CM–AVM and probably represents a coincidental finding.

With the co-occurrence of both neurologic and dermatologic abnormalities, this patient's condition constitutes a neurocutaneous disease. The 5q14.3q15 microdeletions of four other patients were reported to encompass *RASA1*; Table I lists these four patients. Patient 2 of Engels et al. [2009] had no AVMs on cranial MRI but did have a hemangioma on her philtrum. The authors hypothesize that the *RASA1* deletion may account for this vascular malformation. While hemangiomas are not part of the CM–AVM clinical

TABLE I. Patients With Simultaneous Deletions of *MEF2C* and *RASA1*

| Patient | CM–AVM characteristics |
|---|---|
| Engels et al. [2009] Patient 2 | Hemangioma? |
| Le Meur et al. [2010] Case 3 | None |
| Nowakowska et al. [2010] Patient 4 | None |
| Zweier et al. [2010] Patient P4 | None* |
| Current report | Multiple capillary malformations |

[a]Personal communication.

spectrum, the possibility exists that this cutaneous lesion may in fact be a CM. Three other patients with 5q14.3q15 microdeletions encompassing *RASA1* had no reported CM–AVM characteristics. In addition to these four patients, Case 1 of Le Meur et al. [2010] featured a microdeletion whose proximal breakpoint was ~250 kb distal to *RASA1*. This patient had a substernal fistula and two hemangiomas [personal communication]. A combination of a positional effect on *RASA1* and misinterpretation of the dermatologic findings is possible although unlikely.

Of the five patients in Table I with *RASA1* deficiency, only two patients manifest symptoms of CM–AVM, and this assumes that the hemangioma of Patient 2 of Engels et al. is actually a CM. This 40% penetrance drops even lower (20%) if this assumption is incorrect. However, prior research has shown that *RASA1* deficiency does not have low penetrance; two sets of patients demonstrated penetrance of 90% [Eerola et al., 2003; Boon et al., 2005] and 96% [Revencu et al., 2008]. Several reasons might explain the seemingly lower penetrance among the five patients. First, three of these patients (Case 3 Le Meur et al., Patient 4 of Nowakowska et al., and Patient P4 of Zweier et al.) are at a young age when obvious manifestations of *RASA1* deficiency may not have appeared. CMs may appear at birth but also may not appear until childhood [Revencu et al., 2008]; the average age of onset is unknown. Second, any internal vascular malformations in the CNS below the neck will remain undetected in these patients without appropriate imaging. Third, the high penetrance figures published for CM–AVM were determined using populations of patients with *RASA1* mutations, not deletions. The lower penetrance observed in the patients in Table I may suggest some unknown mechanism whose presence or absence in *RASA1* deletions attenuates CM–AVM penetrance. Fourth, CM–AVM has variable expressivity [Eerola et al., 2003; Boon et al., 2005; Hershkovitz et al., 2008]. The CM–AVM disease process may be subtle and go undetected in any patient that manifests with a small number of relatively inconspicuous CMs [Revencu et al., 2008]. Hopefully, in examinations of patients with gross neurologic deficits, the sensitivity for dermatologic abnormalities will increase with the report of this 5q14.3 neurocutaneous syndrome.

## Other Deleted Genes

As discussed in the Introduction Section, research supports *RASA1* and *MEF2C* haploinsufficiency as the etiological basis of this 5q14.3 neurocutaneous syndrome. Haploinsufficiency of the three other genes involved in this patient's microdeletion (*CCNH*, *TMEM161B*, and *COX7C*) are less likely to contribute to the patient's phenotype. *CCNH* codes for cyclin H, a component of CDK-activating kinase, which phosphorylates cyclin-dependent protein kinases involved in cell cycle regulation [Eki et al., 1998]. The function of TMEM161B, a transmembrane protein [Lancet et al., 2008], is unknown. No human pathology has been associated with either *CCNH* or *TMEM161B* deficiency. COX7C is a regulatory subunit of cytochrome c oxidase, a complex in the mitochondrial electron transport chain. Ezugha et al. [2010] identified a patient with a 5q14.3 deletion involving *COX7C* (this deletion was 1.3 Mb proximal to *MEF2C*). This patient was found to have persistent metabolic acidosis and, interestingly, shared some abnormal neurologic features with the aforementioned 19 patients, including mental retardation, hypotonia, absent speech, and seizures. Ezugha et al. [2010] attributed this patient's deficits to *COX7C* haploinsufficiency. The patient reported herein does not have acidosis. Of the 19 previously reported patients who share a common neurologic phenotype with our patient, only two (Patient 4 of Nowakowska et al. and Patient P4 of Zweier et al.) had microdeletions involving *COX7C*. Congenital acidosis was described in neither. As such, *COX7C* deficiency is unlikely to contribute to our patient's abnormalities. On the other hand, one could consider the possibility that the neurologic deficits of Ezugha's patient may be due to a positional effect on *MEF2C*, though this would constitute one of the more distant known positional effects [Kleinjan and van Heyningen, 2005].

## Clinical Implications

The recognition of 5q14.3 neurocutaneous syndrome has clinical implications. In patients with neurologic deficits consistent with *MEF2C* haploinsufficiency, medical providers should evaluate for dermatologic and vascular findings. In patients presenting with CM–AVM and neurologic deficits, suspicion for *MEF2C* haploinsufficiency should be high. In either scenario, aCGH is warranted to investigate for the contiguous deletion of *MEF2C* and *RASA1*.

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