ABSTRACT

BACKGROUND AND PURPOSE: Pathogenic variants in the ACTA2 gene cause a distinctive arterial phenotype that has recently been described to be associated with brain malformation. Our objective was to further characterize gyral abnormalities in patients with ACTA2 pathogenic variants as per the 2020 consensus recommendations for the definition and classification of malformations of cortical development.

MATERIALS AND METHODS: We performed a retrospective, multicentric review of patients with proved ACTA2 pathogenic variants, searching for the presence of malformations of cortical development. A consensus read was performed for all patients, and the type and location of cortical malformation were noted in each. The presence of the typical ACTA2 arterial phenotype as well as demographic and relevant clinical data was obtained.

RESULTS: We included 13 patients with ACTA2 pathogenic variants (Arg179 mutation, n = 11, and Arg179Cys mutation, n = 2). Ninety-two percent (12/13) of patients had peri-Sylvian dysgyria, 77% (10/13) had frontal dysgyria, and 15% (2/13) had generalized dysgyria. The peri-Sylvian location was involved in all patients with dysgyria (12/12). All patients with dysgyria had a characteristic arterial phenotype described in ACTA2 pathogenic variants. One patient did not have dysgyria or the characteristic arterial phenotype.

CONCLUSIONS: Dysgyria is common in patients with ACTA2 pathogenic variants, with a peri-Sylvian and frontal predominance, and was seen in all our patients who also had the typical ACTA2 arterial phenotype.

ABBREVIATIONS: MCD = malformation of cortical development; PMG = polymicrogyria

Heterozygous, autosomal dominant, pathogenic variants in the ACTA2 gene encoding α-2 smooth-muscle actin that replace the arginine at protein position 179 (Arg179) with either histidine, leucine, cysteine, or serine cause a multisystemic smooth-muscle dysfunction syndrome (Online Mendelian Inheritance in Man, 613834; https://www.omim.org). Actin is found in the contractile apparatus of muscle and the cytoskeleton. There are 6 distinct isoforms (α-skeletal, α-cardiac, α-smooth, β-cytoplasmic, γ-smooth, γ-cytoplasmic actin) encoded by 6 different genes.1 Alpha smooth-muscle actin encoded by the ACTA2 gene constitutes the major contractile unit of the vascular smooth muscle expressed by blood vessels.2,3 As part of this ACTA2 syndrome, a distinctive arterial phenotype was described by Munot et al,4 with the phenotype further expanded by D’Arco et al5 to include brain malformative features such as a radial orientation of frontal lobe gyri, flattening of the pons, and bending and hypoplasia of the anterior corpus callosum. Following the diagnosis of an unusual malformation of cortical development (MCD) in our index patient (Online Supplemental Data, patient 9), we reviewed the neuroimaging features of patients with ACTA2 pathogenic variants across 4 tertiary pediatric hospitals.
The location of the dysgyria was noted in each case. All patients also had MR angiograms that were used to subjectively note the presence or absence of a typical arterial phenotype characterized by dilation of the proximal ICAs, abrupt caliber change at the level of terminal ICAs, a straight course of the abnormal ICAs, and absent Moyamoya-like collaterals.

**RESULTS**

Patient demographics and genetic and imaging findings are summarized in the Table and Online Supplemental Data. The cohort consisted of 9 females. The ACTA2 pathogenic variants included the Arg179His mutation (n = 11) and the Arg179Cys mutation (n = 2).

Twelve of 13 patients (92%) had peri-Sylvian dysgyria, with abnormal bifurcation or trifurcation of the Sylvian fissure, which was appreciated rostrally on the sagittal sections (Fig 1A and Fig 2B–E). Ten of 13 patients had frontal dysgyria, with obliquely oriented superior frontal sulci, best appreciated in the axial plane (Fig 1B and Fig 2C–E). Two of 13 patients had generalized dysgyria in addition to the above. This was characterized by involvement of the entire cerebral cortex by an abnormal gyral pattern with variable sulcal depth and orientation (Fig 2E). In 10 patients, the dysgyria was associated with areas of undulated cortex that did not meet the criteria for PMG (Fig 3). Patients 3 and 13 developed seizures following a stroke, yet no other patients had epilepsy. All except 1 patient (patient 13) had the typical ACTA2 arterial phenotype. This patient had normal intracranial imaging features (Fig 2F) except for a variable degree of arterial tortuosity.

**DISCUSSION**

We demonstrate previously under-recognized MCDs in most of our patients with the ACTA2 pathogenic variants in the form of peri-Sylvian and frontal dysgyria. In addition, most of our patients with dysgyria had an undulating appearance of the cortex, which did not meet the criteria for PMG. We term this spectrum of malformations “ACTA2-related dysgyria.” The typical ACTA2 arterial phenotype was noted in all except 1 patient.

The vascular effects of ACTA2 pathogenic variants are attributed to increased smooth-muscle cell proliferation in smaller-diameter muscular arteries and decreased contractility in larger elastic arteries. Histologic specimens from patients with ACTA2 pathogenic variants have shown large intracerebral arteries with marked intimal thickening and smooth-muscle cell proliferation; increased collagen and a relatively milder degree of smooth-muscle cell proliferation in the tunica media; as well as thickened, split, and fragmented internal elastic lamina, which showed less folding compared with that in controls.

In the series published by D’Arco et al, the abnormally oriented frontal lobe gyri were, at the time, aptly termed “abnormal radial gyration.” On review of 6 cases from the article by D’Arco et al, with the addition of a further 7 cases in our series, we have termed the abnormal gyration “dysgyria,” based on the latest 2020 consensus guidelines with this feature not only limited to the frontal lobes but also involving peri-Sylvian regions in most of our patients and generalized distribution in a minority. The peri-Sylvian dysgyria in our series was characterized by an abnormal bifurcation or trifurcation of the Sylvian fissure best appreciated on the sagittal plane. As mentioned earlier, the undulating appearance of the cortex in regions of dysgyria in our study is distinct from the appearance of PMG in that these cases lack the...
small microgyri at chaotic angles that have been described in classic PMG. We, therefore, use the term \textit{ACTA2}-related dysgyria to describe our spectrum of findings.

The structural brain malformations in patients with an \textit{ACTA2} pathogenic variant were initially attributed to either a mechanical effect from “rigid” vessels or abnormal cross-regulation between different isoforms. Before recent evidence confirming otherwise, it was presumed that \(\alpha\)-actin was not expressed in the brain parenchyma; therefore, it would be unlikely for \textit{ACTA2} pathogenic variants to directly influence brain development.\footnote{Subramanian Jan 2022 www.ajnr.org}

While rigid vessels may explain some of the features seen in \textit{ACTA2} pathogenic variants, they do not explain the spectrum of dysgyria that we have described in this study. For instance, histologic specimens show intimal and medial thickening with a relatively spared adventitia, explaining the luminal stenosis, but they do not explain malformations of structures extrinsic to the vascular wall. Recent studies demonstrating \(\alpha\)-actin\footnote{Subramanian Jan 2022 www.ajnr.org} and, more specifically, \textit{ACTA2}\footnote{Subramanian Jan 2022 www.ajnr.org} expression in the brain parenchyma shed light on potential alternate hypotheses for the presence of MCDs in these patients. In 2017, Moradi et al\footnote{Subramanian Jan 2022 www.ajnr.org} described differing roles of \(\alpha\)-, \(\beta\)-, and \(\gamma\)-actin in axon growth, guidance, arborization, and synaptogenesis and demonstrated that all 3 actin isoforms were expressed in motor neurons, with their respective messenger RNAs localizing within axons. Alpha-actin, in particular, was highly expressed in the axonal compartment and axonal branch points, with depletion of \(\alpha\)-actin associated with altered filopodia dynamics, reduced filopodia length, and diminished ability to form axonal collateral branches. Another recent study demonstrated that \textit{ACTA2} was expressed in neural stem cells of embryonic C57BL/6 mice and played an essential role in neural stem cell migration.\footnote{Subramanian Jan 2022 www.ajnr.org}

Furthermore, several studies have shown that knockout of specific actin isoforms leads to compensatory upregulation of other isoforms so that the overall levels of actin are maintained.\footnote{Subramanian Jan 2022 www.ajnr.org} Also, notably, no actin isoform differs from another by more than 7% at the primary amino acid level;\footnote{Subramanian Jan 2022 www.ajnr.org} therefore,
cross-regulation between actin isoforms, especially when there is depletion of one isoform and compensatory up-regulation of other isoforms, may also play a role in *ACTA2* pathogenic variants. These observations may, therefore, help classify *ACTA2*-related dysgyria as a migrational or postmigrational disorder involving the processes of neuronal migration and organization, axonogenesis, and dendritogenesis.

The consistent distribution of dysgyria in the peri-Sylvian regions and frontal lobes is intriguing. One possible explanation may be that developing vessels perform scaffolding and a paracrine signaling function for developing neural cell populations. Indeed, whole-brain MR angiography in our index patient (patient 9) revealed the presence of arterial branches coursing along the abnormally oriented sulci (Fig 4). Recent genetic insights have shown that the embryogenesis of the vascular and nervous systems are closely interlinked and that the axon growth cone and endothelial tip cell respond to growth and guidance cues in similar ways. In addition, there is cross-talk between neural and vascular cells for the purpose of normal development, and signals from both neural and vascular tissue can influence the branching of one another. For instance, neuronal activity has been found to influence cerebrovascular density, vessel branching, and maturation via molecular cues as well as direct cell-to-cell contact of neural cell types with endothelial cells. Similarly, CNS vasculature patterning plays a crucial role in preventing mispositioning of neuronal precursor cells and in providing a scaffold for neuronal migration, axonal projections, and cell soma arrangements in the developing brain. Thus, stiff and noncompliant *ACTA2*-mutant arteries may present a rigid scaffold to the developing brain, resulting in abnormal gyral patterning. Another factor that may contribute to dysgyria includes aberrant tension-induced growth of white matter, influencing folding patterns in a viscoelastic model of the brain, as described in an excellent recent review of the mechanics of cortical folding. Therefore, an interplay of various factors during the

![FIG 4. Anterior cerebral artery branches follow abnormal sulci (arrows).](image)

**Demographics, neuroimaging findings, and clinical presentation**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Mutation</th>
<th>Peri-Sylvian</th>
<th>Frontal</th>
<th>Generalized</th>
<th>Undulating Cortex in Regions of Dysgyria</th>
<th>Presenting Symptom</th>
<th>Seizures</th>
<th>Typical ACTA2 Vascular Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 yr</td>
<td>M</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>Cardiac arrest in early life</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>4 yr</td>
<td>F</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>Stroke-like episodes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>6 yr</td>
<td>F</td>
<td>Arg179His</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Stroke</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>13 wk</td>
<td>M</td>
<td>Arg179His</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Aniridia</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>5</td>
<td>3 yr</td>
<td>F</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Yes</td>
<td>Cardiac symptoms</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>4 yr</td>
<td>F</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Yes</td>
<td>Left hemiparesis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>2 mo</td>
<td>F</td>
<td>Arg179Cys</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Yes</td>
<td>Anisocoria and cataract</td>
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<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>4 yr</td>
<td>M</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>Congenital mydriasis</td>
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<tr>
<td>9</td>
<td>11 yr</td>
<td>F</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
<td>Congenital mydriasis</td>
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<tr>
<td>10</td>
<td>17 yr</td>
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<td>Arg179His</td>
<td>+</td>
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<td>–</td>
<td>Yes</td>
<td>Chronic headaches</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>11</td>
<td>8 yr</td>
<td>F</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Yes</td>
<td>Spastic quadriplegic cerebral palsy, headaches</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>11 yr</td>
<td>F</td>
<td>Arg179His</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Yes</td>
<td>Stroke</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>7 yr</td>
<td>M</td>
<td>Arg179Cys</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>None (screened as part of family)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Note: + indicates present; –, absent; NA, not applicable.
stages of neuronal migration, axonogenesis, and vasculogenesis may each contribute to the patterns of dysgyria that we have described in this article.

CONCLUSIONS

Dysgyria is common in patients with ACTA2 pathogenic variants and has a frontal and peri-Sylvian predominance. Although the underlying mechanisms are yet to be elucidated, recent insights suggest the potential roles of mutant α-actin in neuronal migration and axonogenesis, abnormal cross-regulation between actin isoforms, aberrant neurovascular cross-talk, and an abnormal vascular scaffold, resulting in these malformations.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES