Syndromic and Systemic Diagnoses Associated With Isolated Sagittal Synostosis

Amani A. Davis, BA*
Mostafa M. Haredy, MD†‡
Jennifer Huey, MS*
Hannah Scanga, MS*
Giulio Zuccoli, MD§¶
Ian F. Pollack, MD¶
Mandeep S. Tamber, MD, PhD***
Suneeta Madan-Khetarpal, MD††
Jesse Goldstein, MD†
Suneeta Madan-Khetarpal, MD††
Ken K. Nischal, MD,
FRCOphth*‡‡

Background: Reports of systemic associations in patients with Isolated Sagittal Synostosis (ISS) are sparse. Craniofacial surgeons, and other providers, should be aware that a significant proportion of patients with ISS may have syndromic or systemic involvement. This study investigates the incidence of systemic disease and syndromic diagnosis in a cohort of patients presenting with ISS (ie, patients with sagittal synostosis without other sutureal involvement).

Methods: This study consists of a retrospective review of patients diagnosed with ISS between 2007 and 2017 at a single institution. Patients were divided according to onset (early <1 year, late >1 year) of ISS. Patient notes were examined for congenital anomalies, systemic conditions, and molecular testing. Only patients with isolated sagittal fusion—meaning, patients with sagittal synostosis and no other sutureal involvement—were included.

Results: Three hundred seventy-seven patients met the inclusion criteria: systemic conditions were identified in 188/377 (50%) of them. One hundred sixty-one patients with early onset (Group A), and 216 patients with late onset ISS (Group B) were identified. Systemic involvement was identified in 38% of Group A and 60% of Group B, which was statistically significant ($P < 0.001$). Forty-eight of 377 (13%) of patients had a syndromic diagnosis, and 79% of these were confirmed via genetic testing. Thirty-five percent of patients were diagnosed with central nervous system anomalies and 16% had craniofacial anomalies.

Conclusions: Nearly 50% of the patients initially diagnosed with ISS were found to have some form of systemic involvement. This supports affording full pediatric and genetic evaluation with molecular testing to these children. (Plast Reconstr Surg Glob Open 2019;7:e2540; doi: 10.1097/GOX.0000000000002540; Published online 30 December 2019.)

INTRODUCTION

Craniostenosis (CS) is the premature fusion of one or more cranial sutures and may be syndromic or nonsyndromic.1 CS occurs one in every 2,000–2,500 live births.2 The gold standard for diagnosis is a 3D-CT scan.3 Sagittal CS is the premature fusion of the sagittal cranial suture, resulting in a lengthened cranium in the anterior–posterior direction with stunted growth in the parietal and temporal regions.4 Patients with Isolated Sagittal Synostosis (ISS) have no other sutureal involvement, and account for half of all cases of CS.6,7 Reports of systemic associations in patients with ISS are sparse.8–16 This study investigates the incidence of systemic disease and syndromic diagnosis in a cohort of patients presenting with ISS. Our investigation was inclusive of previously identified (such as Rickets and Noonan syndrome), as well as previously unidentified or underreported (such as seizures, Stickler and Waardenburg) syndromes and systemic findings in patients with ISS.

METHODS

Patients diagnosed with ISS were identified through perusal of clinical databases (pediatric ophthalmology, radiology, and genetics). The gold standard for diagnosis was a 3D-CT scan. Reports of systemic associations in patients with ISS are sparse.8–16 This study investigates the incidence of systemic disease and syndromic diagnosis in a cohort of patients presenting with ISS. Our investigation was inclusive of previously identified (such as Rickets and Noonan syndrome), as well as previously unidentified or underreported (such as seizures, Stickler and Waardenburg) syndromes and systemic findings in patients with ISS.
radiology, neurosurgery, and cleft craniofacial departments) for the years 2007–2017 at a single institution. Our children’s hospital is a major referral center for craniofacial anomalies. All patients included in the study obtained a CT diagnosis of CS. Each patient was then evaluated by the cleft-craniofacial team. Only patients with isolated sagittal fusion—meaning, patients with sagittal synostosis and no other sutural involvement—were included. Patients who developed ISS after a shunting procedure for hydrocephalus or had multisutural CS were excluded. Patients were then divided according to their age at diagnosis of ISS. Group A: early onset (cases diagnosed at ≤ 1 year of age), Group B: late onset (cases diagnosed after 1 year of age). Patient notes were examined for the following data sets: date of birth, age of presentation, age at last follow-up, other congenital anomalies, systemic conditions, syndromic diagnosis, and molecular testing results. The genetic testing protocol at our institution includes SNP, exome, and specific panel testing. Exome testing can be employed as first; second; or third tier testing. First tier testing also includes SNP arrays (combo chip for complete micro arrays with SNP arrays) to determine copy number and copy neutral variation. If phenotype is very clear then a panel is recommended (e.g., Noonan or CTD like Loey-Dietz). Different services at our institution simultaneously phenotype during consultations and management; which includes imaging and biochemical testing. Finally, clinical testing for genetics may be determined by the family history. Statement of IRB approval: IRB#: REN17110211/PRO16110394.

All systemic diagnoses were initially included. Once all were gathered, nonspecific findings or those that were not causative or etiologically related were excluded, such as cerebral palsy, Gastroesophageal reflux disease, Moyamoya disease, caudal regression, G6PD deficiency, congenital nonstationary night blindness, Gaucher, and VACTERL syndromes. Patient information regarding genetic diagnoses was verified by a genetic counselor. IRB approval was obtained before the beginning of this research project. Statistics were conducted using SPSS, and a chi-square test was run to determine a significant difference in the incidence of systemic involvement between Group A and B. None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article.

RESULTS

Three hundred seventy-seven patients with ISS were identified. Systemic conditions were identified in 188/377 of the total cohort. Thirty-eight percent of early onset patients had systemic involvement, and 60% of late onset patients had systemic involvement. Within the 188 patients with systemic involvement, 48 (25%) had an identifiable syndrome. Of these 48, 42 underwent molecular testing. In total, 38/48 syndromes were confirmed via genetic testing (79%). The complete range of syndromic and molecular diagnoses is shown in Table 1.

In the total cohort, 140/377 patients (37%) did not have a syndromic diagnosis but had systemic involvement in one or more organ systems. When statistically analyzed by age of presentation (early/group A or late/group B), the incidence of systemic involvement was significantly higher in the late onset group: 38% in Group A versus 60% in Group B (P < 0.001). Of the 188 patients with systemic and/or syndromic diagnoses, 134/188 had central nervous system anomalies (71%). Looking specifically at these 134 patients, 4% had tethered cord, 11% had hydrocephalus or raised intracranial pressure, 28% had seizures/epilepsy, and 37% had developmental delay. If we look at the entire cohort of ISS patients (n = 377), 4% had raised intracranial pressure or hydrocephalus, 10% had seizures, and 15% had developmental delay. Sixty-one of 377 (16%) patients were diagnosed with other craniofacial anomalies, including cleft palate (9%), torticollis (2%), macrocephaly (4%), microcephaly (1%), and Pierre Robin sequence (1%).

Limb anomalies were identified in 7 patients (1.8%). Urogenital abnormalities were identified in 10 patients (2.6%). We identified 8 patients with a diagnosis of ISS and a clinical diagnosis of RASopathy (Table 2): 6 diagnosed with Noonan syndrome and 2 with cardiofaciocutaneous syndrome (CFC). Five of these patients had molecular confirmation (3 Noonan 2 CFC). We describe 3 patients with metabolic disorders (Table 2), 2 of whom had Rickets. Four patients tested positive for single-gene mutations. Fifteen patients with chromosomal abnormalities were identified (Table 1). Three of the 15 (20%) patients identified with chromosomal abnormalities had chromosomal aberrations previously reported in patients with CS. Twenty of 377 patients (5%) with autism spectrum disorder (ASD): 16 with Autism, and 4 with Asperger’s.

DISCUSSION

Single case reports and/or small case series have reported associations between ISS and the syndromes listed in Table 3. Specifically, our cohort contained Turner syndrome (n = 1), craniofrontonasal dysplasia (n = 1), rickets (n = 3), RASopathy (Noonan and CFC syndromes), osteogenesis imperfecta (n = 1), ectodermal dysplasia (n = 1), and Loey-Dietz (n = 1). We did not identify patients diagnosed with several of the syndromes previously reported in association with ISS (Table 3). However, we describe ISS in association with conditions not previously described in the literature (Table 3), including stickler syndrome (n = 1). ISS is seldom included as a presenting feature of single gene CS syndromes—like Apert and Crouzon—but has been linked to chromosomal aberrations. However, we identified 3 patients diagnosed with ISS and craniofacial syndromes: Pfeiffer (n = 1), Craniofrontonasal Dysplasia (n = 1), and Saethre-Chotzen (n = 1).

Sagittal synostosis and RASopathy, particularly Noonan syndrome, have been reported together previously, in association with the following genes: SHOC-2, KRAS, BRAF, and PTPN. CFC has also been previously reported in patients with ISS. Both of our patients diagnosed with CFC had mutations in BRAF. Three of 6 patients in our cohort who were clinically diagnosed with Noonan syndrome had mutations in KRAS, BRAF,
and PTPN respectively, the 3 remaining patients did not reveal any mutations, but the panel used did not analyze SHOC-2. We recommend that patients with a Noonan-like phenotype undergo a RASopathy panel, inclusive of the SHOC-2 gene and or whole exome sequencing.

Table 1. Syndromes and Chromosomal Abnormalities in Total ISS Cohort

| Type                              | Sex (M/F) | Genetic Testing Results                                                                 |
|-----------------------------------|-----------|-----------------------------------------------------------------------------------------|
| Neuro/neurocutaneous: total: 2    |           | Linear nevus sebaceous syndrome: 1 total                                                |
| Acrocallosal syndrome: 1 total    |           |                                            |
| RASopathies: total: 8             |           | Cardiofaciocutaneous syndrome: 2 total                                                  |
| Noonan syndrome: 6 total          |           |                                            |
| Noonan syndrome: 3 total          |           |                                            |
| Metabolic disorders: 3            |           | Autosomal recessive rickets: 1 total                                                    |
| Connective tissue disorders: total| 4         | Loeys-Dietz syndrome: 1 total                                                           |
|      4                            |           | Type II Stickler syndrome: 1 total                                                      |
|      4                            |           | Multiple exostoses Type I: 1 total                                                      |
| Craniofacial disorders: total: 3  |           | Pfeiffer syndrome: 1 total                                                              |
| Craniofrontonasal dysplasia: 1 total|       |                                             |
| Saethre-Chozten suspect: 1 total  |           |                                            |
| Single gene mutations: total: 4   |           | KCNT1 mutation; mitochondrial disorder, (complex IV deficiency): 1 total                |
| FLNB and ADAMTS10 mutations: 1    |           |                                            |
| MESP2 mutation: 1 total           |           |                                            |
| Connexin 26 (GJB2): 1 total       |           |                                            |
| Skull dysplasia: 1 total          |           |                                            |
| Pigmentary disorders: total: 1    |           | Waardenburg syndrome: 1 total                                                           |
| Chromosome (micro array) syndromes: total: 4 |   | DiGeorge syndrome: 1 total                                                              |
|                                      |           |                                            |
| Klinefelter syndrome: 1 total     |           |                                            |
| Cohen syndrome (suspect): 1 total  |           |                                            |
| Other Total: 2                    |           | Ectodermal dysplasia: 1 total                                                           |
| Chromosomal abnormalities: total: 15 |         | Heterotaxy syndrome: 1 total                                                           |
| of 5q and 7q: 1 total             |           |                                            |
| 12q21 deletion: 1 total           |           |                                            |
| Ring chromosome 8: 2 total        |           | Deletion of 11.99 Mb of DNA from 18p11.21pter and 448.2 kb of DNA from 18q23pter; duplication of genetic material from 18p22.23, duplication of 1.44 Mb of DNA from 18p22.121p24.3. |
| 16p micro array aberration(s) 5 total |       |                                            |
| 16p micro array aberration(s) 5 total |       |                                            |
| 16p micro array aberration(s) 5 total |       |                                            |
| 16p micro array aberration(s) 5 total |       |                                            |
| Partial trisomy 3q/monosomy 18p: 1 total |       |                                            |
| 15q13.3 deletion: 1 Total         |           |                                            |
| Chromosome 2 deletion: 1 total    |           |                                            |
| 1q21.1 deletion: 1 total          |           |                                            |
| 1p36.12 duplication: 1 total      |           |                                            |
| Chromosome 2 deletion, 15q duplication: 1 total |       |                                            |

and PTPN respectively, the 3 remaining patients did not reveal any mutations, but the panel used did not analyze SHOC-2. We recommend that patients with a Noonan-like phenotype undergo a RASopathy panel, inclusive of the SHOC-2 gene and or whole exome sequencing.
Rickets has been described in association with CS previously.20,21 We identified a single patient with ectodermal dysplasia, which has previously been reported with ISS.13 Given that more than half of patients reported in Lin’s study diagnosed with ectodermal dysplasia also had ISS, there is likely a causative relationship, though the exact nature is unclear.

**Single Gene Mutations**

Of the patients with single gene mutations, 1 presented with epilepsy, Chiari I malformation, plagiocephaly, and microcephaly. A syndromic diagnosis was not made, but he tested positive for a \( KCNT1 \) mutation, which is associated with epilepsy. Another patient was found to have a mutation in the \( MESP2 \) gene, which has been implicated in spondylo-costal dysostosis type 2. Our patient did not have the typical phenotype of this condition, so it may be that we are seeing a milder/different end of the spectrum of phenotype caused by the \( MESP2 \) mutation. We also identified a single patient with an \( FLNB \) mutation. Though they were not found in our patient, mutations in the \( FLNB \) gene may cause severe bone dysplasias.28 Missense mutations in this gene are also associated with Larsen syndrome and Boomerang Dysplasia, a lethal form of osteochondrodysplasia.29,30

**Chromosomal Abnormalities**

Three of the 15 (20%) patients identified with chromosomal abnormalities had chromosomal aberrations previously reported in patients with CS: Kleefestra,30 45,X (Turner syndrome)20 and 22q deletion (DiGeorge Syndrome),32,33 of which only 45,X has been reported in a patient with ISS (6%). We identified several noteworthy anomalies which so far have not been described in patients with only ISS, such as a 1p36.12 duplication, which to date is of unknown significance. However, deletions of the same region of chromosome 1p36 constitute a deletion syndrome. It is associated with developmental delay, short stature, prominent forehead, congenital heart disease, hypotonia, and early death.34,35 Another patient had a 1q21.1 deletion, which is also associated with developmental delay, schizophrenia, microcephaly, cardiac abnormalities, and cataracts.35–37 Another patient presented with a de novo microdeletion in 16p13.1, spanning the \( NTAN \) and \( NDE1 \) genes. Developmental delay, epilepsy, short stature, dysmorphic appearance, and behavioral problems are known to accompany this mutation. This disease has been clinically and molecularly diagnosed in fewer than 15 patients worldwide.38 We also identified 2 patients with 16p13.2 deletions.39,40 One case report describes a patient with 16p13.2 and Pfeiffer syndrome without a diagnosis of CS.16 We have identified a patient with the same mutation, diagnosed with ISS, but not Pfeiffer syndrome. In total, our cohort contains 5 patients with 16p aberration(s) on microarrays. The fact that only 6% of the chromosomal aberrations described in our study have been previously reported in patients with ISS supports increased karyotyping and utilization of molecular cytogenetics in patients diagnosed with ISS who have systemic involvement.

**Systemic Findings**

In our cohort, 38/377 (10%) ISS patients had seizures. Eighteen percent of these seizure were febrile. The association between CS and seizures has been previously described.26,27 However—to the best of our knowledge—this is the first report suggesting that 1/10 patients with ISS will suffer from seizure activity. Our cohort contains 20 patients with ASD: 16 with Autism, and 4 with Asperger’s. ASD has

---

**Table 2. Systemic Findings**

| Systemic Finding                  | Includes                                                                 | Total Affected |
|----------------------------------|-------------------------------------------------------------------------|----------------|
| Seizures                         | Febrile and afebrile                                                    | 38 (10%)       |
| Cardiac abnormalities            | ASD, VSD, PFO, PDA, murmur, arteriovenous malformation, aortic stenosis, | 31 (8%)        |
| Renal/urogenital abnormalities   | Renal aplasia, horseshoe kidney cryptorchidism, hypospadias             | 19 (5%)        |
| Structural neurological abnormalities | Tethered cord, hydrocephalus                                           | 20 (5%)        |
| Developmental delay              | Speech, global, cognitive                                              | 50 (15%)       |
| Autinsic spectrum disorder       | Autism, aspergers                                                      | 20 (5%)        |
| Cleft palate                     | Submucous cleft palate                                                 | 35 (9%)        |
| Constitutional                   | Micro/macrocephaly, Pierre Robin sequence, failure to thrive, short stature | 35 (9%)        |
| Musculoskeletal/limb abnormalities | Polydactyly, syndactyly, torticollis, clubfeet                         | 15 (4%)        |

**Table 3. Syndromes Associated with ISS, Previously Reported, and Unreported**

| Previsouly Reported Syndromes Appearing in Patients with ISS | Syndromes Appearing Outside Our Cohort | Previsouly Unreported Syndromes Found in Our ISS Cohort |
|--------------------------------------------------------------|----------------------------------------|---------------------------------------------------------|
| Turner syndrome                                              | Crouzon’s syndrome                     | Stickler syndrome                                       |
| Craniofrontonasal dysplasia                                  | Frank-ter Haar syndrome                | Kleefestra                                              |
| Rickets                                                      | Ellis-van Creveld syndrome             | Waardenburg                                             |
| Noonan                                                       | Sensenbrenner                          | Cohen syndrome                                          |
| Osteoginesis imperfecta                                      | Pfeiffer-type Cardiocranial syndrome   | Acralcallosal syndrome                                  |
| Ectodermal dysplasia                                         | Carpenter syndrome                     | Linear Sebaceous Nievus syndrome                         |
| Turner syndrome                                              |                                        | Pfeiffer syndrome                                       |
| Loeps-Dietz syndrome                                         |                                        | DiGeorge syndrome                                       |
| Cardiofacioctaneous syndrome                                 |                                        |                                                         |
previously been described in patients with CS, and may be due to genetic, epigenetic, and environmental factors.22 Autism is associated with both sporadic and syndromes like Fragile X and 22q11.2 deletion syndrome.42–44 Of the 20 patients identified with ASD, 4 had an additional syndromic diagnosis: CFC, 15q13.3 deletion, 16p.13.3 deletion, and congenital stationary night blindness.

In our cohort, the incidence of developmental delay was 13%. The association between developmental delay and CS is noted in many publications, and the incidence of neurocognitive deficits in patients with sagittal synostosis has been reported to be 3–5 times that of the unaffected population.45–52 Developmental delay in patients with single suture CS (SSC) has been described in studies and case reports,2,4,18,31,34,51 but there have been few studies of developmental delay in patients with ISS.46,47,49,54 Additionally, a control-matched study of 209 patients with SSC reported that 3-year-olds with SSC scored lower on the Griffiths mental development scales than the control cohort who did not have a diagnosis of CS.53 A study of operated ISS patients revealed patients with ISS and developmental delay who underwent surgical repair demonstrated a reduction in their developmental delay as evidenced by performance on the Griffiths scale.54 But this is controversial.55 In the ISS population, developmental delay in language and speech are frequently reported.46,54 In our cohort, 16 of the 50 patients diagnosed with developmental delay were also diagnosed with speech delay. Abnormal speech and language development have been reported in 1/1.7 of patients with nonsyndromic SSC, and as high as 37% in metopic-sagittal synostosis patients.55 Visual deficits have also been reported. Abnormalities in fixation shift have been reported in patients with ISS. One study inclusive of 15 patients with sagittal synostosis, reports 11/15 patients (73%) with ISS demonstrated abnormal fixation shift.55 Like developmental delay, visual function has been shown to improve postoperatively in patients with CS. In particular, patients with sagittal CS demonstrated a deficit in gross locomotor function which resolved after surgical correction of deformity.54 We recommend patients with ISS undergo full pediatric and ophthalmic evaluations in addition to their craniofacial assessment, considering that surgical intervention has been shown to ameliorate visual, cognitive, or developmental delays.54

To the best of our knowledge, this is the largest series investigating the incidence of syndromes/systemic involvement in patients with ISS. We report 188/377 patients with systemic involvement, and 13% of the total cohort had a syndromic diagnosis. The proportion of ISS patients who underwent testing was small (20%), but the pediatric patient registry uncovered a large proportion of syndromes and genetic mutations underlying their sagittal synostosis diagnosis. Even though ISS is the most common form of CS, physicians and scientists have not yet identified a genetic cause for most forms of ISS. On the other hand, syndromic forms of CS—though less common—are known to be caused by >60 associated genetic mutations.56 Since genetic testing has resulted in the discovery of novel mutations related to ISS etiology,10,12,18,24,25,34,57 we suspect that increased genetic testing of these patients may result in better knowledge regarding the etiology of ISS.

CONCLUSIONS

We suggest that our finding that almost half of patients with ISS have some sort of systemic involvement warrants that children diagnosed with ISS undergo complete pediatric and evaluations with appropriate utilization of molecular cytogenetics of array-CGH as well as molecular testing for pathogenic variants in the genes by single gene, gene panel, or whole exome sequencing. A statistically significant higher incidence of systemic involvement was found in the late onset ISS subgroup, which supports long-term monitoring of patients with early and late onset ISS. Many children with ISS are followed by a primary care pediatrician. Craniofacial surgeons, and other providers, should be aware that a significant proportion of patients with ISS may have syndromic or systemic involvement. Such knowledge may result in better treatment strategies for these children.
14. Bendon CL, Fenwick AL, Hurst JA, et al. Frank-ter haen syndrome associated with sagittal craniosynostosis and raised intracranial pressure. *BMC Med Genet*. 2012;13:104.

15. Phi JH. Slit ventricle syndrome and early-onset secondary craniosynostosis in an infant. *Am J Case Rep*. 2014;15:246–253.

16. Hufnagel RB, Zimmerman SL, Krueger LA, et al. A new frontonasal dysplasia syndrome associated with deletion of the SIX2 gene. *Am J Med Genet A*. 2015;170:487–491.

17. Cohen MM, Opitz JM, Reynolds JF, et al. Craniosynostosis update 1987. *Am J Med Genet*. 1988;31:99–148.

18. Addissie YA, Kotecha U, Hart RA, et al. Craniosynostosis and Noonan syndrome with KRAS mutations: expanding the phenotype with a case report and review of the literature. *Am J Med Genet A*. 2015;167:2657–2663.

19. Cohen MM. Craniosynostosis in the Ulrich-Turner syndrome. *Am J Med Genet*. 1990;35:289–290.

20. Jaszcuk P, Rogers GF, Guzman R, et al. X-linked hypophosphatemia and sagittal craniosynostosis: three patients requiring operative cranial expansion: case series and literature review. *Childs Nerv Syst*. 2016;32:887–891.

21. Vega RA, Opalak C, Harshberger RJ, et al. Hypophosphatemic rickets and craniosynostosis: a multicenter case series. *J Neuropsychiatr Pediatr*. 2016;18:679–700.

22. Chen H. Sagittal craniosynostosis associated with chromosome abnormalities with a brief review on craniosynostosis. *Atlas of Genetic Diagnosis and Counseling*. 2017;2525–2536.

23. Komatsuzaki S, Aoki Y, Niihori T, et al. Mutation analysis of the SHOC2 gene in Noonan-like syndrome and in hemolytic malignancies. *J Hum Genet*. 2010;55:801–809.

24. Kratz CP, Zampino G, Krieg M, et al. Craniosynostosis in patients with Noonan syndrome caused by germline KRAS mutations. *Am J Med Genet A*. 2009;149A:1036–1040.

25. Ueda K, Yaito M, Niihori T, et al. Craniosynostosis in patients with rasopathies: accumulating clinical evidence for expanding the phenotype. *Am J Med Genet A*. 2017;173:2346–2352.

26. Jazayeri MA, Jensen JN, Lew SM. Craniosynostosis following hemispherectomy in a 2.5-month-old boy with intractable epilepsy. *J Neuropsychiatr Pediatr*. 2011;8:450–454.

27. McCarthy JG, Glaser SG, Cutting CB, et al. Twenty-year experience with early surgery for craniosynostosis. *Plast Reconstr Surg*. 1995;96:296–298.

28. Lu J, Liang G, Lenkinski R, et al. Filamin B mutations cause chondrodysplasia in skeletal development. *Hum Mol Genet*. 2007;16:1661–1675.

29. Bicknell LS, Morgan T, Bonafe L, et al. Mutations in FLNB cause boomerang dysplasia. *J Med Genet*. 2005;42:e43.

30. Greally MT, Jewett T, Smith WI, Jr, et al. Lethal bone dysplasia in a fetus with manifestations of atelosteogenesis I and boomerang dysplasia. *Am J Med Genet*. 1993;47:1086–1091.

31. Sibbesen ELC, Jespersgaard C, Alosi D, et al. Ring chromosome 9 in a girl with developmental delay and dysmorphic features: case report and review of the literature. *Am J Med Genet A*. 2013;161:1447–1452.

32. De Silva D, Duffy P, Booth P, et al. Family studies in chromosome 22q11 deletion: further demonstration of phenotypic heterogeneity. *Clin Dysmorphol*. 1995;4:294–303.

33. 22q11.2 deletion syndrome - Genetics Home Reference - NIH. U.S. National Library of Medicine. https://ghr.nlm.nih.gov/condition/22q112-deletion-syndrome. Accessed July 11, 2018.

34. Hiraki Y, Fujita H, Yamamori S, et al. Mild craniosynostosis with 1p36.3 trisomy and 1p36.3 deletion syndrome caused by familial translocation (t(Y1). *Am J Med Genet A*. 2006;140:1773–1777.

35. Heilestedt HA, Ballif BC, Howard LA, et al. Population data suggest that deletions of 1p36 are a relatively common chromosome abnormality. *Clin Genet*. 2003;64:310–316.

36. Bernier R, Steinman KJ, Reilly B, et al; Simons VIP consortium. Clinical phenotype of the recurrent 1q21.1 copy-number variant. *Genet Med*. 2016;18:341–349.

37. Christiansen J, Dyck JD, Elyas BG, et al. Chromosome 1q21.1 contiguous gene deletion is associated with congenital heart disease. *Circ Res*. 2004;94:1429–1435.

38. Stockman J. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. *Yearbook of Pediatrics*. 2010;2010:300–302.

39. INSERM. Orphanet: Syndrome de microd. Orphanet: Achromatopsia. https://www.orpha.net/consor4/01/www/cgi-bin/OC_Exp.php?lng=FR&Expert=261236. Accessed July 11, 2018.

40. Hempel M, Brugués NR, Wagenstaller J, et al. Microdeletion syndrome 16p11.2;p12.2: clinical and molecular characterization. *Am J Med Genet A*. 2009;149A:2106–2112.

41. Ettinger N, Williams M, Phillips JA 3rd. Variable expressivity and clinical heterogeneity can complicate the diagnosis and management of pfeiffer syndrome. *J Craniofac Surg*. 2013;24:1829–1832.

42. Waye MM, Cheng HY. Genetics and epigenetics of autism: a review. *Psychiatry Clin Neurosci*. 2018;72:228–244.

43. Yu TW, Berry-Kravis E. Autism and fragile X syndrome. *Semin Neurol*. 2014;34:258–265.

44. Weng PL, Miller JS, Depolo LM, et al. 22q11.2 duplication syndrome: elevated rate of autism spectrum disorder and need for medical screening. *Mol Autism*. 2016;7:27.

45. Bartlett S. Speech, cognitive, and behavioral outcomes in nonsyndromic craniosynostosis. *Yearbook of Plastic and Aesthetic Surgery*. 2007;2007:26.

46. Shipster C, Hearst D, Somerville A, et al. Speech, language, and cognitive development in children with isolated sagittal synostosis. *Dev Med Child Neurol*. 2002;45.

47. Virtanen R, Korhonen T, Fagerholm J, et al. Neuropsychological sequelae of scaphocephaly. *Pediatrics*. 1999;103:791–795.

48. Da Costa AC, Anderson VA, Holmes AD, et al. Longitudinal study of the neurodevelopmental characteristics of treated and untreated nonsyndromic craniosynostosis in infancy. *Childs Nerv Syst*. 2013;29:985–995.

49. Christian E, Imahiyerobo T, Johns A, et al. 310 Predictors of preoperative developmental delay in nonsyndromic sagittal craniosynostosis. *Neurosurg*. 2016;63:189.

50. Chieffo D, Tamburrini G, Massimi L, et al. Long-term neuropsychological development in single-suture craniosynostosis treated early. *J Neurosurg Pediatr*. 2010;5:232–237.

51. Speltz ML, Collett BR, Wallace ER, et al. Intellectual and academic functioning of school-age children with single-suture craniosynostosis. *Pediatrics*. 2015;135:e615–e623.

52. Naran S, Miller M, Shakir S, et al. Nonsyndromic craniosynostosis and associated abnormal speech and language development. *Plast Reconstr Surg*. 2017;140:262–269e.

53. Nelson M, Quinonez S, Ackley T, et al. Multiple congenital anomalies and developmental delay in a boy associated with a de novo 16p13.3 deletion. *Am J Med Genet A*. 2011;155:612–617.

54. Bellew M, Liddington CM, Chumas P, et al. Preoperative and postoperative developmental attainment in patients with sagittal synostosis: 5-year follow-up. *J Neurosurg Pediatr*. 2017;11:121–126.

55. Ricci D, Vasco G, Baranello G, et al. Visual function in infants with non-syndromic craniosynostosis. *Dev Med Child Neurol*. 2007;49:574–576.

56. Aoyohkawa NR, Solomon BD, Muenke M. Impact of genetics on the diagnosis and clinical management of syndromic craniosynostoses. *Childs Nerv Syst*. 2012;28:1447–1463.

57. Latanzi W, Bukvic N, Barba M, et al. Genetic basis of single-suture synostoses: genes, chromosomes and clinical implications. *Childs Nerv Syst*. 2012;28:1301–1310.