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## Organization of Prenatal Care in Orofacial Clefts and Suspected Robin Sequence: A European Survey

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**Abstract:** Advances in prenatal imaging and genetic testing have improved the detection of orofacial anomalies, allowing for early diagnosis and comprehensive counseling. This study aims to provide an overview of current prenatal care practices for orofacial clefts and/or suspected Robin sequence (RS) across European countries and to identify disparities to inform future improvements. A cross-sectional survey was distributed to health care professionals affiliated with the European Reference Network CRANIO, collecting data on prenatal imaging, genetic testing, counseling, and termination of pregnancy. Responses were obtained from 31 health care professionals in 27 hospitals across 17 European countries. All participating countries have some sort of prenatal screening program. Ultrasound examination was performed at 1 or 2 timepoints during pregnancy, with varying techniques used to assess orofacial structures. Fetal MRI was performed in 59% of centers, primarily for multiple (severe) anomalies. Centers utilizing specific imaging techniques reported fewer missed diagnoses. Prenatal genetic testing was available in 96% of centers, with array-based copy number variation and whole-exome sequencing performed in 59% and 52% of centers, respectively. Nearly half of the centers provided multidisciplinary counseling, with team composition and session frequency varying widely. Pregnancy termination for orofacial clefts or micro-/retrognathia was not legal in 7 countries. Termination rates and trends differed across centers. In conclusion, variability exists in prenatal care for orofacial clefts and/or suspected RS across Europe, particularly in imaging techniques, genetic testing, and pregnancy termination practices. These findings highlight the need for standardized guidelines and equitable access to multidisciplinary care to optimize outcomes for affected pregnancies.

**Key Words:** Europe, orofacial clefts, prenatal diagnosis, robin sequence, survey

Orofacial clefts are among the most common congenital anomalies, affecting ~1 in 700 live births worldwide.<sup>1</sup> These anomalies can lead to significant challenges, such as feeding difficulties, speech and hearing impairments, and psychosocial issues.<sup>2</sup> In certain cases, orofacial clefts are associated with additional congenital anomalies or syndromes, including Robin sequence (RS), which may complicate postnatal management. RS is characterized by a triad of micrognathia, glossoptosis, and airway obstruction, often occurring alongside cleft palate.<sup>3,4</sup> Infants with RS require specialized care due to airway and feeding difficulties.

Advances in prenatal imaging, particularly detailed ultrasound and fetal MRI, have improved our ability to detect orofacial clefts and signs of micrognathia or retrognathia during pregnancy.<sup>5–8</sup> In addition, other structural anomalies are better visualized. Parallel to these imaging advancements, developments in prenatal genetic testing techniques have expanded our knowledge of genetic variants associated with these anomalies, enabling detailed prenatal diagnoses.<sup>9</sup> Consequently, parents can now receive comprehensive information early in pregnancy about the presence of orofacial clefts and suspected RS, as well as associated anomalies or genetic variations as part of a syndromic diagnosis. This early insight allows parents and health care professionals to make

more informed decisions about whether to continue the pregnancy and to better prepare for the course of pregnancy, delivery, and postnatal care.

Because of technical innovations, prenatal screening and diagnostics have advanced significantly over the last 2 decades, yet there is no clear overview of how prenatal care for orofacial clefts and suspected RS is organized across European countries. Given the complexity of prenatal decision-making in cases involving orofacial clefts and/or suspected RS, the ERN CRANIO (European Reference Network for rare and/or complex craniofacial anomalies and ear, nose, and throat disorders) scientific committee has recognized the need for a comprehensive understanding of how prenatal care is organized across Europe.<sup>10</sup>

The aim of this survey study is to provide an overview of the current organization of prenatal care for pregnancies diagnosed with an orofacial cleft or suspected RS across European countries. This study will also serve as a foundation for future discussions on existing disparities in prenatal care, ultimately guiding efforts to optimize prenatal care practices and create more uniform care.

## MATERIALS AND METHODS

This cross-sectional study utilized an online survey developed by the author panel and further refined by local clinicians and the scientific committee of the ERN CRANIO. The final survey contained a mixture of a maximum of 59 multiple-choice and open-ended questions, tailored based on respondents' answers (Supplement 1, Supplemental Digital Content 1, <http://links.lww.com/SCS/H609>). Most questions were structured to prompt respondents to provide information about practices at their clinic, assuming standardized definitions and management within the clinic. The survey was created and distributed using Microsoft Forms, an online survey platform. The survey was available only in English.

The survey was sent to member hospitals and supporting partners within the ERN CRANIO cleft workstream (i.e., those involved in the care of infants with clefts and suspected Robin sequence). The network encompasses professionals such as clinical geneticists, gynecologists, nurse specialists, oral and maxillofacial surgeons, otolaryngologists, pediatricians, (pediatric) plastic surgeons, and psychologists. Initial invitations were sent on October 11, 2024. Responses were collected anonymously. A reminder was sent on October 28, 2024 to increase response rate. During the ERN CRANIO 9<sup>th</sup> annual meeting in Gdansk, Poland (November 6–8, 2024), a link to the survey was distributed to all participants.

Both complete and incomplete responses were included in the analysis, except for those deemed unreliable by the authors (e.g., only respondent characteristics were completed or <50% of the survey was filled out). Multiple responses from one center were allowed, given the fact that for example an oral and maxillofacial surgeon may not be able to answer all questions regarding prenatal genetic testing.

Approval for this study was obtained from the UMC Utrecht (ethics code: 24U-1905). This study does not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO). It, therefore, does not require approval from an accredited medical ethics committee in the Netherlands. However, in the UMC Utrecht, an independent quality check has been carried out to ensure compliance with legislation and regulations. All participants consented that their responses could be used for research purposes.

## RESULTS

### Respondents

A total of 31 health care professionals from 27 ERN member/partner hospitals spread across 17 European countries completed the survey, with no exclusions made. An overview of the respondents' characteristics can be found in Supplemental Table 1 (Supplemental Digital Content 2, <http://links.lww.com/SCS/H610>). Most respondents originated from the Netherlands (n = 5, 16%) and Spain (n = 4, 13%). The majority of the respondents were specialists in the field of gynecology/obstetrics (32%), oral and maxillofacial surgery (16%), or plastic surgery (16%) (Fig. 1). Other fields included genetics (7%), nurse specialists (13%), pediatrics (13%), and psychology (3%). All except 2 respondents, who worked in a general hospital and a specialized pediatric hospital, were affiliated with university hospitals. In nearly half of the centers (n = 12, 44%), a specialized multidisciplinary team was available. The incidence of prenatally detected orofacial clefts and/or micro-/retrognathia varied significantly, ranging from 1 to 2 cases per year to more than 21 cases annually (Supplemental Table 1, Supplemental Digital Content 2, <http://links.lww.com/SCS/H610>).

### Prenatal Screening Programs

All countries in this survey reported the existence of some form of prenatal screening program. Programs were introduced as early as the 1970s or as late as the 2000s. In 53% of the countries, prenatal screening is fully covered by social health insurance. In Austria, the costs are covered by private or additional health insurance, or out-of-pocket payment. Ultrasound examinations are carried out in Austria at cost price and paid for out-of-pocket. In the United Kingdom, the costs are covered by the National Health Services (NHS). In Hungary and Poland, only essential ultrasound examinations are typically covered; more advanced imaging or genetic screening, such as noninvasive prenatal testing (NIPT), fetal MRI, or in-depth genetic testing, may require private or additional health insurance or out-of-pocket payment. In Sweden, there is regional variability, particularly in the maternal age threshold for trisomy screening coverage. In many countries (n = 13), prenatal care is provided both in centralized centers (i.e., university hospitals) and in dedicated clinics (i.e., clinics offering prenatal care only). For example, in France there is a prenatal diagnostic center for pregnancies with pathology. In this dedicated center, multidisciplinary care is provided. In other countries, such as Latvia, prenatal screening is performed in dedicated clinics; however, high-risk patients are referred to university hospitals. Respondents did not report if there was a difference in reimbursement for prenatal care offered in centralized centers or in dedicated clinics.

### Imaging

In 71% of the countries (n = 12), a prenatal screening ultrasound is routinely performed at a single timepoint (15–16 wk or 18–22 wk gestation). In 29% of the countries (Germany, Hungary, Latvia, the Netherlands, and Poland), 2 screening ultrasounds are routinely performed (11–14 wk and 18–22 wk gestation). In case of abnormalities, diagnostic ultrasound is frequently performed by gynecologists/obstetricians (78% of the centers) and sonographers (33% of the centers) (Supplemental Table 2, Supplemental Digital Content 2, <http://links.lww.com/SCS/H610>). Several centers reported techniques for evaluating the palate (Supplemental Table 3,

Supplemental Digital Content 2, <http://links.lww.com/SCS/H610>), including the “the equal sign”, “Batman sign”, “search the mouth bell”, and specific sagittal or axial transverse views. For mandible assessment, the maxilla-nasion-mandible (MNM) angle was reported frequently. Other techniques reported include the inferior facial angle (IFA), “jaw index”, and “mandible length”. One center published these techniques.<sup>11</sup>

Fetal MRI, performed on indication in 16 centers (59%), is typically conducted between 28 and 32 weeks gestation. Common indications include severe micrognathia, microsomia, suspected central nervous system anomalies, airway-compressing masses, or syndromic conditions.

Figure 2 illustrates the range of prenatally missed orofacial cleft and micro-/retrognathia cases (estimated number). The estimated number of prenatally missed cases of orofacial cleft and micro-/retrognathia per center can be found in Supplemental Table 3 (Supplemental Digital Content 2, <http://links.lww.com/SCS/H610>). Centers with lower rates of prenatally missed cases reported more frequent use of specific techniques for assessing the palate and mandible.

## Genetic Testing

Prenatal genetic testing is available in 96% of the centers ( $n=26$ ), with clinical geneticists or gynecologists (or both) conducting counseling for genetic testing in 96% of the centers (Table 2, Supplemental Digital Content 2, <http://links.lww.com/SCS/H610>). Testing is almost always (71%–100%) recommended for orofacial clefts in several centers, particularly in Belgium, France, Hungary, Ireland, Latvia, the Netherlands, Slovenia, and Spain. Respondents indicated that genetic testing was offered less frequently in cases of micro-/retrognathia, except for one center in France. This center reported offering genetic testing “very frequently” for clefts (51%–70% of cases), and offering genetic testing “almost always” for micro-/retrognathia (71%–100% of cases). Factors as cleft severity, additional anomalies, family history, and findings on diagnostic imaging play an important role in decision-making. Maternal age seems to play a limited role (i.e., for 32%–35% of the respondents, it is a decisive factor). In general, parents frequently or almost always opt for genetic testing for orofacial clefts or micro-/retrognathia ( $n=20$  versus  $n=17$ , respectively). In Austria, Norway, and Poland parents opt for genetic testing less frequently (10%–30%).

Advanced techniques such as array-based copy number variation (CNV) and (trio-) whole-exome sequencing (WES) are performed in 59% and 52% of the centers that perform genetic testing, respectively (Supplemental Table 2, Supplemental Digital Content 2, <http://links.lww.com/SCS/H610>). Relevant findings lead to additional counseling sessions in half of the respondents' centers, focusing on perinatal care planning and termination options (both in 67% of the centers) or additional imaging such as detailed anomaly ultrasounds or MRI (30%). Notably, most respondents ( $n=25$ , 81%) reported the absence of national guidelines for genetic testing in prenatal orofacial clefts or micro-/retrognathia diagnoses.

## Counseling

In nearly half (44%) of the respondents' centers, prenatal counseling is provided by a multidisciplinary team comprising specialists such as oral and maxillofacial surgeons, clinical geneticists, plastic surgeons, gynecologists/obstetricians, pedia-

tricians, nurse specialists, and speech-language pathologists. Counseling frequency varies, with sessions offered once (13%), 2 to 3 times (35%), or on an as-needed basis (35%). Three centers (Austria, Finland, and Latvia) lack follow-up procedures to ensure parental understanding. Adequate interdisciplinary support was reported by 74% of respondents, especially in centers with multidisciplinary teams, although opinions varied within one such center.

## Termination of Pregnancy

In 7 countries (Belgium, Finland, Ireland, Poland, Portugal, Slovenia, and the United Kingdom), termination of pregnancy (TOP) for orofacial clefts or micro-/retrognathia is not permitted according to the survey respondents. France allows TOP for micro-/retrognathia only. Legal time limits for TOP ranged from 18 to 24 weeks, with Sweden having the strictest limit (18 wk) and France the most permissive (42 wk). TOP for these diagnoses was rare, occurring in 0% to 30% of cases. Trends in TOP vary across centers, with some centers (in the Netherlands, Slovenia, Spain, and Sweden) reporting an increase over time, whereas others (in Hungary, Norway, and Spain) observed a decline.

## DISCUSSION

This cross-sectional survey study was designed to provide a comprehensive overview of the organization of prenatal care for pregnancies diagnosed with orofacial clefts and/or micro-/retrognathia across European countries. Although all surveyed countries have some form of prenatal screening program, including voluntary noninvasive prenatal testing (NIPT) and standard fetal anatomy ultrasound examination (s), the findings reveal notable variability in screening performance of imaging, genetic testing, and counseling practices, alongside marked disparities in termination of pregnancy regulations.<sup>12–16</sup> This could be caused by differences in procedure performance and coverage of health care costs. An in-depth analysis of the regulations per country was beyond the scope of this survey, but such an effort would certainly provide important additional information and might serve as a foundation for a new European guideline to reduce practice variation between countries.

As expected, the number of prenatally detected orofacial clefts and micro-/retrognathia per year differed between the expertise centers. Therefore making it questionable whether smaller-sized centers have the same experience in prenatal care as larger-sized centers. Yet, when looking at the availability of standardized local institutional guidelines for prenatal care, this is lacking in both the smaller-sized centers as the larger-sized centers. In addition, the number of prenatally missed cases did not seem to differ between smaller-sized and larger-sized centers, according to this survey.

The results in this study revealed marked variations in the estimated rate of prenatally missed cases of orofacial clefts and/or micro-/retrognathia, despite 2D or 3D ultrasound and fetal MRI being commonly used diagnostic tools. These findings suggest that detection rates vary between centers, which may be caused by many factors not assessed in depth in this survey. One possible explanation for this variability is that some respondents may have misinterpreted the survey question regarding the number of prenatally missed cases. Specifically, it seems that some participants reported the number of cases detected prenatally (e.g., 95% for cleft lip, 5% for iso-

lated cleft palate) rather than the number of missed cases. In contrast, the variability observed in this survey aligns with findings in the literature, which indicate international differences in prenatal detection rates for orofacial clefts. For instance, the detection rate for CL ± P has been reported as 71.7% in Denmark, 89.5% in England, and 44.6% in Switzerland.<sup>8,17,18</sup>

It seems that centers using specific ultrasound techniques for assessing the palate and mandible reported fewer missed cases, suggesting that advanced imaging protocols improve diagnostic accuracy. For example, techniques such as the “equal sign” or axial transverse ultrasound view for palate assessment and the MNM angle or IFA for mandible evaluation seem to provide critical diagnostic information.<sup>11,19–21</sup> It remains unclear why centers have not adopted these methods and criteria more widely. However, discrepancies persist even among centers using similar imaging modalities, indicating that factors such as performer-experience, equipment quality, and training protocols may also play a role. Notably, in current literature, it seems that larger sample sizes and, therefore, more experience lead to a significant improvement in the test’s predictive accuracy. In a study with sample sizes involving more than 3000 patients, the predictive accuracy of the ultrasound ranged from 63% to 75%. In contrast, a study with 141 patients has shown a prediction accuracy of only 31%.<sup>22</sup> Furthermore, fetal MRI is often considered a complementary tool for diagnosing orofacial clefts, particularly cleft palate, in fetuses at risk.<sup>23–25</sup> Although some of the participating centers in this survey reported utilizing fetal MRI, this study did not assess its additional value or its impact on the number of prenatally missed cases in detail. Consequently, no conclusions can be drawn on its role in improving diagnostic accuracy. In addition, it is likely that cases of orofacial cleft or micro/retrognathia missed on initial ultrasound are not referred to tertiary centers for further evaluation with detailed ultrasound or fetal MRI. Moreover, cost and resource constraints are also likely contributors to the marked variations in detection rates, particularly in countries where advanced imaging is not covered by social health insurance. For example, in Hungary and Poland, only essential ultrasounds are typically funded, and parents may bear the financial burden of additional imaging.

The widespread availability of prenatal genetic testing, with whole-exome sequencing (WES) and array-based copy number variation (CNV) analysis commonly used, underscores the advanced capabilities of many centers in this field. Although these tests identified genetic variants, they did not significantly alter pregnancy management or treatment decisions in this study. The high rate of parental agreement to testing suggests that families value genetic information, possibly for postnatal planning or future family planning decisions. However, lower agreement rates in certain countries may reflect cultural, socioeconomic, or educational disparities. Besides, the majority reported that their country lacks a national guideline on performing (prenatal) genetic testing in cases with orofacial clefts or micro-/retrognathia. Yet, there are European guidelines available, through the ERN CRANIO, for both orofacial clefts and Robin sequence. These guidelines recommend that all cases should be referred to a clinical geneticist for counseling on prenatal genetic testing (especially with new techniques being developed and working towards the availability of WGS).<sup>26,27</sup>

Termination of pregnancy (TOP) for orofacial clefts or micro-/retrognathia was not permitted in 7 European countries according to the respondents in this survey. Yet, these findings

do not align with current regulations in some of these countries.<sup>28–32</sup> In many countries, voluntary termination is permitted up to a certain gestational age, and afterwards it is only allowed for specific (medical) indications. It is likely that conditions such as orofacial cleft and micro- or retrognathia are not considered valid medical indications in these contexts. The prohibition of termination of pregnancy in certain countries may reflect underlying religious or cultural influences. Although this study did not specifically investigate the role of religion, it is plausible that religious or sociopolitical factors influence these regulations. The variability in legal limits for TOP, ranging from 18 weeks (Sweden) to 42 weeks (France), also suggests significant ethical and cultural differences across countries. Further studies are needed to explore these influences on the availability of TOP and parental decision-making, providing context for national and cross-border differences in prenatal care options. Not only legal and religious issues play an important role in the decision to terminate a pregnancy but also the parental attitude towards orofacial clefts or micro-/retrognathia.<sup>33</sup> This view is influenced by family, friends, and medical counseling provided by a health care professional.<sup>34</sup> According to previous literature, parents who opted for a follow-up counseling session were less likely to terminate.<sup>35</sup> In this present study, this was not examined.

Counseling practices varied widely. More than half of the centers lacked a formal protocol, which raises concerns about the consistency and quality of information provided to parents. This inconsistency could potentially influence parental decisions, including whether to continue the pregnancy. Moreover, differences in the frequency of counseling sessions may lead to varying levels of parental understanding and preparedness, which could have long-term implications for both families and health care systems. Furthermore, a multidisciplinary cleft or craniofacial team was present in only 44% of the centers. Counseling by multidisciplinary teams is a strength, as it ensures comprehensive input from various specialists. This is supported by our findings, as adequate interdisciplinary support was more often reported by centers with multidisciplinary teams. Yet, based on this survey no differences in the number of terminated pregnancies were seen between the participating centers with and without a protocol or multidisciplinary cleft or craniofacial team, but differences may exist when investigating this issue more in depth. In addition, previous studies reported that of those who had a prenatal diagnosis and counseling, up to 96% felt well prepared and/or considered prenatal diagnosis a benefit, especially when counseled by a multidisciplinary team.<sup>36–38</sup>

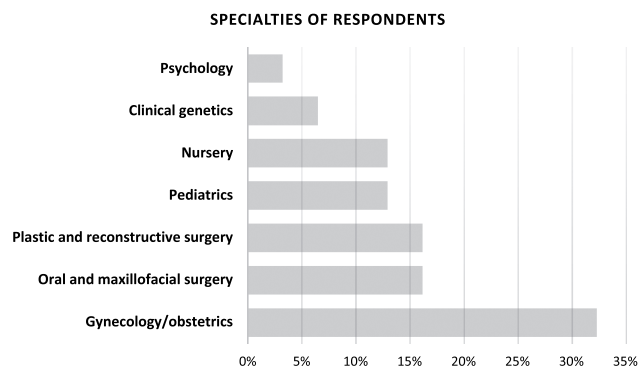
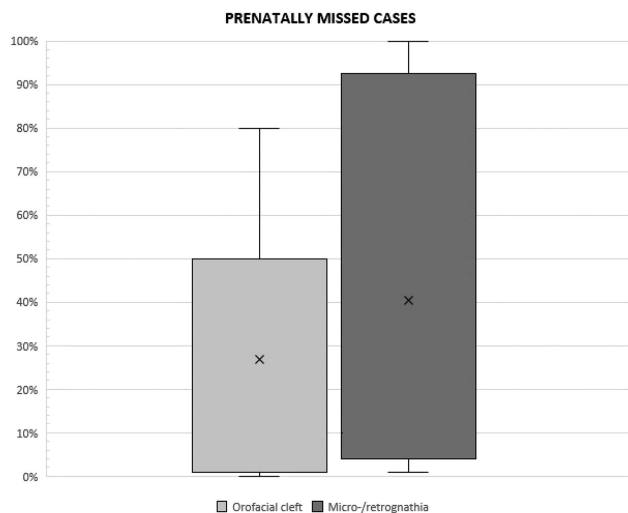


FIGURE 1. Distribution of specialties of respondents.



**FIGURE 2.** The range of prenatally missed cases (orofacial cleft versus micro-/retrognathia).

Several limitations of this study have to be addressed. First, the sample size was small due to the decision to distribute the survey exclusively to member hospitals and supporting partners from the ERN CRANIO cleft workstream. Although the aim was to gather responses from all European countries affiliated, this was not achieved despite sending reminders and distributing the survey during an annual meeting. As a result, the sample may not be fully representative. In addition, in some cases, only a single center from a given country completed the survey. One could question the extent to which these results are generalizable to national practice, as variation likely exists between centers within the same country. Moreover, it was not explicitly mentioned whether respondents should answer individually or on behalf of their entire cleft or craniofacial team. As a consequence, multiple responses were obtained from 3 centers, which resulted in discrepancies in answers to some questions. Similarly, multiple centers from the same country participated, leading to inconsistencies in responses to questions about national regulations or guidelines. In addition, some questions may—in retrospect—not have been formulated clearly enough. For instance, it seemed unclear for some respondents that we wanted to know how many cases with an orofacial cleft or micro-/retrognathia were missed prenatally. Consequently, some respondents reported the number of cases detected prenatally (e.g., 95% for cleft lip, 5% for isolated cleft palate) instead of the missed cases. Furthermore, the survey was available only in English, which may have affected how some questions were interpreted. Lastly, the reliance on self-reported data may introduce bias, as respondents might overestimate the quality of care provided in their centers. The strengths of this survey study are that it is the first questionnaire gaining insight in the current practices in prenatal care in Europe, and its broad geographic scope, which ensures a comprehensive overview of these current practices in different regions.

## CONCLUSION

Despite several limitations, the results confirm that substantial disparities in the organization of prenatal cleft and craniofacial care remain across Europe. This study under-

scores the need for harmonized prenatal care practices across Europe, with a focus on improving screening and diagnostic accuracy, and standardizing counseling protocols. Up-to-date (inter)national clinical practice guidelines on this subject are lacking and a multidisciplinary cleft or craniofacial team for counseling is not available in some of the participating reference centers. Addressing these gaps requires a coordinated effort among clinicians, researchers, and policymakers to ensure equitable, high-quality care for affected pregnancies. Standardizing practices and fostering partnerships are essential steps toward a more unified European approach to prenatal care. Future efforts should include consensus meetings to align and improve the organization of prenatal care across Europe.

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## Impact of SMAD6 Variants on Neurodevelopment in Craniosynostosis

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**Background:** Some pathogenic variants in Smad6 are implicated in midline craniosynostosis, particularly in metopic synostosis. These variants increase the risk of both non-syndromic and syndromic presentations. Craniosynostosis, whether treated surgically or not, can be associated with developmental delays.

**Methods:** The authors aimed to assess developmental outcomes in children with craniosynostosis carrying a Smad6 variant. A cohort of children who underwent craniosynostosis surgery at the national reference center for craniosynostosis at Lyon University Hospital (2018–2023) was studied. Children with Smad6 variants were followed postsurgery to evaluate their neuropsychological development. Evaluations were conducted by a multidisciplinary team comprising neurosurgeons, clinical geneticists, and neuropsychologists.

**Results:** Among 249 patients with craniosynostosis, 11 were identified with Smad6 variants. Of these, 7 presented with

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**Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The authors report no conflicts of interest.

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