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ORIGINAL ARTICLE

AXIN2-related oligodontia-colorectal cancer syndrome with cleft palate as a possible new feature

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Abstract

Background: Pathogenic variants in *AXIN2* have been associated with tooth agenesis, colon polyps, and colon cancer. Given the rare nature of this phenotype, we set out to collect additional genotypic and phenotypic information.

Methods: Data were collected via a structured questionnaire. Sequencing was performed in these patients mostly due to diagnostic purpose. A little more than half of the *AXIN2* variant carriers were identified by NGS; other six were family members.

Results: Here, we report 13 individuals with a heterozygous *AXIN2* pathogenic/likely pathogenic variant who have a variable expression of oligodontia-colorectal cancer syndrome (OMIM 608615) or oligodontia-cancer predisposition syndrome (ORPHA 300576). Three individuals from one family also had cleft palate, which might represent a new clinical feature of *AXIN2* phenotype, also given the fact that *AXIN2* polymorphisms have been found in association with oral clefting in population studies. *AXIN2* has already been added to multigene cancer panel tests; further research should be conducted to determine whether it should be added to cleft lip/palate multigene panels.

Tiina Kahre and Katrin Õunap contributed equally.

Conclusion: More clarity about oligodontia-colorectal cancer syndrome, about the variable expression, and associated cancer risks is needed to improve clinical management and to establish guidelines for surveillance. We collected information about the surveillance that was advised, which might support clinical management of these patients.

KEYWORDS

AXIN2, cancer predisposition syndrome, cleft palate, oligodontia

1 | INTRODUCTION

Heterozygous pathogenic variants (PV) in *AXIN2* are the genetic cause of oligodontia-colorectal cancer syndrome (OMIM 608615) or oligodontia-cancer predisposition syndrome (ORPHA 300576). Oligodontia-colorectal cancer syndrome is an autosomal dominant disorder with an estimated prevalence of <1:1,000,000 (Orphanet). It has been known for some time that pathogenic variants in *AXIN2* are also associated with tooth agenesis (Lammi et al., 2004).

Tooth agenesis is defined as the congenital absence of one or more teeth, excluding wisdom teeth. Patients with tooth agenesis can be classified as having hypodontia (1 to 6 teeth missing) or oligodontia (6 or more teeth missing) (Bilgin, 2018). Although this combined dental and colorectal neoplastic phenotype may come as a surprise clinically, in general, animal models have shown that genes associated with dental development or odontogenesis can be involved in cancer development (Cobourne et al., 2009).

AXIN2 gene is located on chromosome 17 and consists of 11 exons (Figure 1g). The Axin2 protein encoded

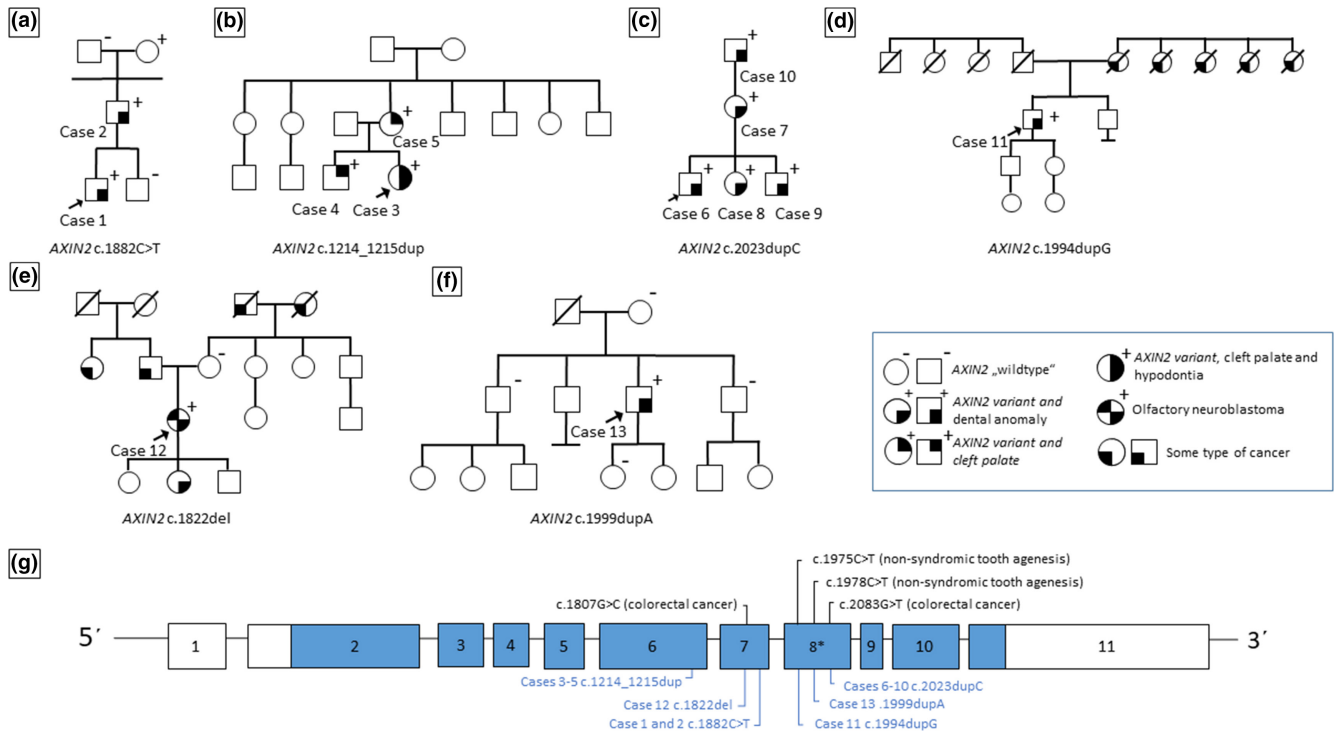

FIGURE 1 Pedigrees of all investigated families. (a) Family 1 (Estonia)—Cases 1 and 2 carrying *AXIN2* c.1882C > T variant; (b) Family 2 (Estonia)—Cases 3–5 carrying c.1214_1215dup variant; (c) Family 3 (Norway)—Cases 6–10 carrying c.2023dupC variant; (d) Family 4 (US)—Case 11 carrying c.1994dupG variant; (e) Family 5 (US)—Case 12 carrying c.1822del variant; (f) Family 6 (The Netherlands)—Case 13 carrying c.1999dupA variant. (g) *AXIN2* gene structure. Our cohort Cases are marked in blue (below the gene exons) and 4 missense variants of unknown significance (VUS) are marked in black above the gene exons. *Variant hot spot region.

by *AXIN2* gene consists of 843 amino acids and is part of the canonical Wnt or Wnt/β-catenin pathway, being its feedback inhibitor. Wnt pathway signaling is important in cell proliferation, differentiation, and homeostatic self-renewal and when dysregulated, is associated with colorectal cancer development (Hlouskova et al., 2017). The association with colorectal cancer was first described by Liu (2000), and in particular, *AXIN2* somatic variants have been reported in microsatellite instable colorectal tumors (Liu, 2000). Two years later, a large Finnish family with colon polyps and cancer was reported carrying the *AXIN2* PV c.1966C > T, p.Arg656* (Lammi et al., 2004). Still, the exact role of all *AXIN2* somatic and germline gene variants observed in colorectal and other cancers remains to be clarified (Mazzoni & Fearon, 2014). With respect to its role in oligodontia, *AXIN2* disease-causing variants particularly inhibit the development of permanent teeth and specifically posterior molars, but do not significantly affect the development of deciduous or primary teeth. During tooth development, *AXIN2* is expressed in enamel knots and dental mesenchyme. The failure of tooth development is probably linked to increased signaling of Wnt/β-catenin pathway in the mesenchyme in case of carrying *AXIN2* pathogenic variant (Jarvinen et al., 2018). As Wnt pathway is also important in craniofacial morphogenesis, *AXIN2* variants have been associated with facial clefts in humans as well (Letra et al., 2012). Although mostly known for affecting teeth and the colorectal system, PVs in *AXIN2* can clinically also manifest as ectodermal dysplasia (abnormal development of the skin, hair, nails, or sweat glands) (Beard et al., 2019).

Given the rare nature of the syndrome, the full phenotype spectrum and its risks remain to be established. For example, a recent case report suggested to include olfactory neuroblastoma and gastric adenoma as part of germline *AXIN2* phenotype (Macklin-Mantia et al., 2020). The same patient (Case 12) reported is part of this cohort. Another patient (Case 11) of this cohort has been published recently (Macklin-Mantia & Riegert-Johnson, 2020). More data are clearly needed. Therefore, we set out to collect additional genotype and phenotype information and information on current clinical management of families. Here, we report on 13 individuals from six families who carry a heterozygous *AXIN2* variant and differ in clinical expression of the oligodontia-colorectal cancer syndrome. Interestingly, we identified cleft palate (CP) as a possible new feature of the syndrome. Cleft palate is the main feature our cohort differs from the other two mentioned in Table 1, and we think it might be a new clinical feature, and it just might not be completely penetrant.

2 | STUDY GROUP AND METHODS

The Research Ethics Committee of the University of Tartu has approved this study. In addition, the study was approved by Mayo Clinic's institutional review board. In Norway, patients signed Oslo University Hospital's declaration of consent, which was approved by the data protection officer at Oslo University Hospital.

Data were collected via a structured questionnaire (Supplementary data), which was sent to all the known clinicians caring for *AXIN2* gene carriers in hospitals that are part of the European Reference Network (ERN) for patients with one of the rare genetic tumor risk syndromes (GENTURIS) as well as from the Mayo Clinic and the Boston Children's Hospital (USA) (ERN GENTURIS website). In our cohort of 13 *AXIN2* carriers, we had eight males and five females from 4 to 95 years of age. All the patients were Caucasian origin, 11 of them from Europe and two from North America. Clinical features, molecular genetic profile, and follow-up are shown in Table 1, where each individual has been given a case number.

Seven of the *AXIN2* carriers (Cases number 1, 3, 4, 6, 11, 12, and 13) were identified by next-generation sequencing (NGS) method, and other six carriers were family members. Sequencing was performed in these patients mostly due to diagnostic purpose: hypo- or oligodontia, polyps, cancer or due to cleft palate in Family 2. The remaining patients were family members of patients with a known *AXIN2* variant in whom the *AXIN2* variant was detected by Sanger sequencing. For NGS library preparation, different capture-based or amplicon-based protocols, for example NexteraFlex for Enrichment (Illumina) or Haloplex Target Enrichment System (Agilent), were used. In Case 1, the *AXIN2* variant was detected through whole genome sequencing (WGS) in a research project. In Cases 3 and 4, TruSight One Expanded (Illumina) panel with 6700 genes and in Case 6 ectodermal dysplasia and hypodontia panel of 34 genes was used. In Cases 11, 12 the diagnosis was made using commercial available NGS cancer panels (70 and 84 genes respectively), and in Case 13, the *AXIN2* variant was found with a whole-exome sequencing (WES)-based colorectal polyposis panel, which included 13 known colorectal polyposis syndromes.

Sequencing was performed on NextSeq500, NovaSeq6000, or HiSeq X Ten (Illumina). All targeted regions were sequenced with ≥50× depth. WGS was sequenced with the mean coverage of ≥30 depth.

Most of the patients were detected in a routine clinical setting. Cases 3 and 4 were found in the cohort of 4704 Estonian patients investigated by Illumina's TruSight One Expanded panel due to different clinical reasons revealing a frameshift variant; no other disease-causing indels, duplications, deletions, stop, or missense variants were

TABLE 1 Clinical and molecular data of all investigated *AXIN2* Cases and summary of most important publications.

Type of data	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Family number	Family 1	Family 1	Family 2	Family 2	Family 2	Family 3	Family 3	Family 3
Demographics								
Sex	M	M	F	M	F	M	F	F
Current age (years)	10 years	41 years	6 years	4 years	26 years	20 years	50 years	22 years
Ethnicity	Estonian	Estonian	Estonian	Estonian	Estonian	Norwegian	Norwegian	Norwegian
Testing indication	Research setting (SRS)	Segregation analysis	Diagnostic setting (Pierre-Robin sequence)	Diagnostic setting (cleft palate)	Segregation analysis	Diagnostic setting (oligodontia)	Segregation analysis	Segregation analysis
Clinical features								
Phenotype (dysmorphology)	N	N	Pierre-Robin sequence	Bilateral cleft palate	Bilateral cleft palate	N	N	N
Oligodontia	+	+	–	–	–	+	–	+
No of missing teeth	8	14	2	–	1 impacted tooth	22	2	8
Eyes	N	N	N	N	N	N	N	N
Ectodermal dysplasia	–	–	–	–	–	–	–	–
Gastrointestinal polyps	n.d.	+	n.d.	n.d.	n.d.	+	+	+
Type and no of polyps	n.d.	1 tubular adenoma	n.d.	n.d.	n.d.	Two tubular adenomas, 1SSP, 1HP	Many tubular adenomas and HPs	One tubular adenoma, 1SSP, 1HP
Colorectal cancer	–	–	–	–	–	–	–	–
Other cancers	–	–	–	–	–	–	–	–
Other health problems	–	–	Epilepsy	–	–	–	–	IBS
Molecular genetic findings								
cDNA (NM_004655.4)	c.1882C>T	c.1882C>T	c.1214_1215dup	c.1214_1215dup	c.1214_1215dup	c.2023dupC	c.2023dupC	c.2023dupC
Protein change	p.(Arg628Trp)	p.(Arg628Trp)	p.(Gly406Argfs*53)	p.(Gly406Argfs*53)	p.(Gly406Argfs*53)	p.Arg675ProfsTer32	p.Arg675ProfsTer32	p.Arg675ProfsTer32
Detection method	WGS	Sanger	NGS	NGS	Sanger	NGS	Sanger	Sanger
Type of mutation	Missense	Missense	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift
Clinical significance	VUS	VUS	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic
Other genetic findings	–	–	–	–	–	–	–	–
Follow-up and treatment								
Colonoscopy interval	From 18 years	Once a year	From 18 years	From 18 years	Follow-up not started yet	Once a year	Once in 2 years	Once in 2 years

TABLE 1 Continued

Type of data	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Other investigations	–	–	–	–	–	Gastroscopy at 25 years	–	Gastroscopy at 25 years
Specific treatment	–	–	–	–	–	–	–	–

Type of data	Case 9	Case 10	Case 11 [12]	Case 12 [11]	Case 13	Summary	Lammi et al. (2004)	Beard et al. (2019)
Family number	Family 3	Family 3	Family 4	Family 5	Family 6			
Demographics							11 cases/17 individuals	Four cases/four individuals
Sex	M	M	M	F	M			
Current age (years)	15 years	95 years	65 years	51 years	65 years			
Ethnicity	Norwegian	Norwegian	American	American	Dutch			
Testing indication	Segregation analysis	Segregation analysis	Diagnostic setting	Diagnostic setting (cancer)	Diagnostic setting			
Clinical features								
Phenotype (dysmorphology)	N	N	N	N	N			
Oligodontia	–	–	–	–	–	**Four out of 13 (30.8%)**	11 out of 11 (100%)	Four out of four (100%)
No of missing teeth	2	4	3[a]	4[a]	4		Eight and more	n.d.
Eyes	N	N	N	N	Sparse eyebrows		n.d.	n.d.
Ectodermal dysplasia	–	–	–	–	–		n.d.	n.d.
Gastrointestinal polyps	n.d.	+	+	+	+	**Eight out of 13 (61.5%)**	Six out of 12 (50%)	Four out of four (100%)
Type and no of polyps	n.d.	Polyposis of the colon	57 polyps in colon	One gastric adenoma and one HP in colon	Polyps in the sigmoid colon and rectum		Different types, numbers and parts of intestine	Different types, numbers and parts of intestine
Colorectal cancer	–	–	–	–	Adenocarcinoma coecum at 62 years	**One out of 13 (7.7%)**	One case (54 years) had adenocarcinoma of the hepatic flexure (5.9%)	One case (43 years) had transverse colon cancer (25%)

(Continues)

TABLE 1 Continued

Type of data	Case 9	Case 10	Case 11 [12]	Case 12 [11]	Case 13	Summary	Lammi et al. (2004)	Beard et al. (2019)
Other cancers	–	–	Skin cancer at the age of 60 years, prostate adenocarcinoma at 62 years	Olfactory neuroblastoma at 49 years	Abdominal superficial melanoma at 61 years		n.d.	n.d.
Other health problems	–	–	–	–	Rheumatoid arthritis, glaucoma, hypertension, obstructive sleep apnea		n.d.	n.d.
Molecular genetic findings								
cDNA (NM_004655.4)	c.2023dupC	c.2023dupC	c.1994dupG	c.1822del	c.1999dupA		c.1966C > T	c.1972delA
Protein change	p.Arg675ProfsTer32	p.Arg675ProfsTer32	p.Asn666fs	p.Leu608Phefs*81	p.Ser667Lysfs*40		p.Arg565*	p.Ser658Alafs*31
Detection method	Sanger	Sanger	NGS	NGS	NGS			
Type of mutation	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift		Stop mutation	Frameshift
Clinical significance	Likely pathogenic	Likely pathogenic	Likely pathogenic/ pathogenic	VUS	Pathogenic		Pathogenic	Likely pathogenetic
Other genetic findings	–	–	–	*NF1* VUS	–			
Follow-up and treatment								
Colonoscopy interval	From 18 years	Last at 70 years	n.d.	Once in 2 years	Once in 2 years			
Other investigations	–	Last rectoscopy at 89 years	–	–	Gastroscopy once in 3 years			
Specific treatment	–	Subtotal colectomy at 70 years	Radiation therapy	Radiation therapy and surgery	Subtotal colectomy at 62 years, pembrolizumab due to metastasis			

Abbreviations: HP, hyperplastic polyp; N, normal; n.d., no data; SRS, Silver–Russell syndrome; SSP, sessile serrated polyp; VUS, variant of unknown significance.

[a]Estimates.

found in *AXIN2* gene in this cohort. Case 12 was found on screening 3000 unselected cancer patients. In other cases, we do not have additional information about cohort sizes. Sanger validation was done in Cases 1, 3, and 13.

3 | RESULTS

Thirteen *AXIN2* PV carriers from six families are included in the study, and their data are shown in Table 1 and Figure 1. Eight were male and five were female with ages ranging from 4 to 95 years. Among them, four were children (≤18 years), who were tested due to clinical indications (failure to thrive, hypodontia, and/or CP). Eleven cases were from Europe and two from North America. The North American patients were thought to be of European descent. Probably, in most cases AXIN2 variants were inherited, although we have no clear evidence. We are not aware of any de novo cases.

The most common clinical feature was either hypo- or oligodontia ranging from 2 to 22 missing teeth (Table 1 and Figure 2). Four patients (30.8%) had at least eight permanent teeth missing, eight (61.5%) had gastrointestinal polyps, and three (23.1%) had some type of cancer. Cancer types involved melanoma, unknown type of skin cancer, olfactory neuroblastoma, and prostate and cecal adenocarcinoma. Olfactory neuroblastoma has recently been linked to *AXIN2* phenotype (Macklin-Mantia et al., 2020). Unfortunately, we did not have specific information about some family members in context of cancer. In a few cases, we saw dysmorphic phenotype. Case 1 has a clinical diagnosis of Silver–Russell syndrome (SRS, OMIM 186860), which is not associated with the found *AXIN2* variant. Case 3 has (operated) bilateral CP, microretrognathia, microglossia with glossoptosis, and two missing teeth. In addition, Case 3 has epilepsy, which is probably not associated with the found *AXIN2* variant. The younger brother of Case 3 (Case 4) and her mother (Case 5) as well have CP (operated) and the mother has one impacted tooth.

The *AXIN2* gene variants reported were almost all pathogenic or likely pathogenic frameshift variants, three of these have not been described before in ClinVar

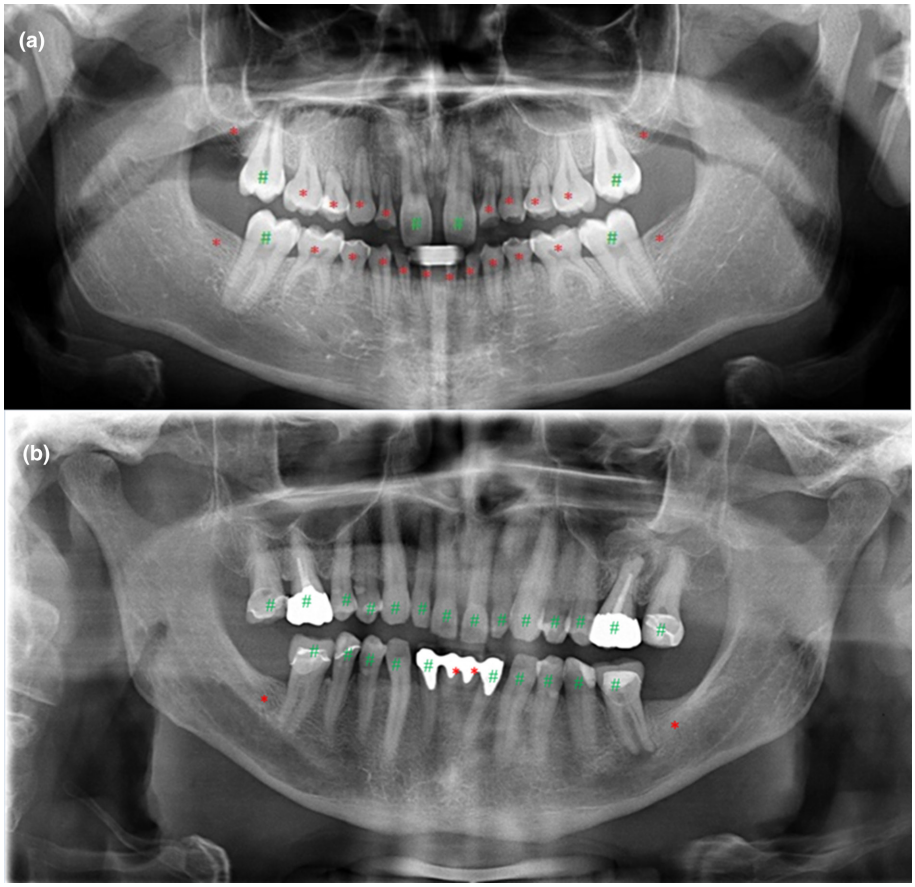

FIGURE 2 (a) Panoramic image of Case 6 at the age of 14 years. He shows congenital absence of 22 permanent teeth (*). As a consequence deciduous teeth have not been exfoliated. Only six permanent teeth are present (#). (b) Panoramic image of Case 13 at the age of 64 years. He shows congenital absence of four permanent teeth (*), 31 and 41 (lower central incisors), as well 37 and 47 (posterior molars in the lower jaw). The persistent deciduous central incisors have been extracted and replaced by a bridge, including teeth 42–41–31-32. Present permanent teeth are also shown (#).

and HGMD Professional databases (c.1214_1215dup, c.1999dupA, and c.2023dupC) (ClinVar database, HGMD Professional database). Most of the variants were located in exon 8, where also the mutation hotspot lies (Figure 1g). Only one missense variant, c.1882C > T, was detected in our cohort (Cases 1 and 2; Figure 1a). This variant has an extremely low allele frequency in normal populations worldwide (gnomAD All VAF 0,017%; 48 alleles out of 282,360). Some in silico prediction programs (SIFT, MutationTaster, Provean) predict this variant as damaging while others (PolyPhen2, Align GVGD) assess this as benign. It is likely that this variant is not completely penetrant, and in the absence of RNA or functional studies, the actual effect is unknown. As the patient and his father (Cases 1 and 2) have oligodontia and no other potential disease-causing variants were detected using WGS, this missense variant could still be associated with the disease, but at the moment, the clinical significance still remains unknown until further data. Variant c.1822del interpretation has recently been changed from pathogenic to VUS. At the moment, repeated genetic testing with clinical RNA testing for further investigation is pending.

In terms of surveillance and follow-up, we aimed to propose a surveillance schedule by gathering information about the clinical management and surveillance that was advised to the patients.

4 | DISCUSSION

Our cohort of 13 *AXIN2* PV carriers confirms the variation in phenotype between families and individual patients. With very few patients reported, the clinical phenotype of *AXIN2* PV is not well understood, so it is likely that new features will be added as more patients are found. Interestingly, we observed three cases of CP in one of the families.

At the moment of writing this article, there were 40 ACMG class 3–5 *AXIN2* variants in HGMD database: 21 are pathogenic or likely pathogenic and 19 are classified as variant of unknown significance (VUS). About half (24) of these variants are associated with polyposis, colorectal cancer, and/or oligodontia. Thirty-three are either nonsense or missense variants, and others include small insertions or deletions and splicing variants. None of the total of 21 *AXIN2* germline pathogenic or likely pathogenic variants reported in HGMD database have been associated with cleft palate so far (HGMD Professional database). In ClinVar, 44 pathogenic or likely pathogenic variants of *AXIN2* have been reported (Clinvar database). Although CP can run in families as a separate trait and could be unrelated to the *AXIN2* variant, the Wnt pathway is known to be important in craniofacial morphogenesis in animal models (B. Liu et al., 2010). In addition, *AXIN2* polymorphisms have been found to be associated with oral clefts in two independent population studies by Letra et al. (2012); (Letra et al., 2009). These authors also provided some biological evidence in support of *AXIN2*s role in clefting. They observed co-localization of Axin2 with cleft-associated Irf6 protein in epithelium and demonstrated *AXIN2* gene expression during murine palatogenesis (Letra et al., 2012). Taken together, this suggests that CP could be part of the oligodontia-colorectal cancer syndrome phenotypic spectrum. However, more data are needed to confirm or refute this hypothesis. Taking the family history of cancer in oral cleft patients is already important because of the association with *CDH1*-associated hereditary diffuse gastric cancer (Frebourg et al., 2006). In our opinion, the possible association with *AXIN2* adds to that reason.

Although we still do not have any official and published European guidelines for this syndrome, cancer and polyp surveillance in our cohort has been almost homogenous. Given the rareness of the syndrome, clinical recommendations with respect to cancer risk management are expert-opinion based and typically modeled after guidelines for other colorectal cancer and polyposis syndromes.

In the National Comprehensive Cancer Network (NCCN) guidelines, colonoscopy is suggested from the age of 25–30 years every 2–3 years if negative. If polyps are found, every 1–2 years. Surgery is indicated when the polyp burden becomes unmanageable with colonoscopy (NCCN guidelines). Recently, part of this cohort was discussed within ERN GENTURIS. Experts including a few of the authors suggested to perform colonoscopy every 2 years and add gastroduodenoscopy every 3 years, or more frequently depending on endoscopic findings, to the surveillance scheme. The reason for the latter was the known involvement of Axin2 in the Wnt pathway that is also dysregulated in APC-gene-associated familial adenomatous polyposis (FAP) where such surveillance is recommended. Clearly further information is needed to support the guidelines for the management of *AXIN2* patients.

In summary, our study confirms the variable phenotype of individuals with germline *AXIN2* pathogenic or likely pathogenic variants and suggests that cleft palate could be a part of the syndrome phenotype. Oligodontia-colorectal cancer syndrome is still mostly unknown by clinicians. It is of utmost importance to raise awareness in the medical society (including dentists and orthodontists) and to educate patients on the risk for different types of cancer. Taking thorough family history of cancer and gastrointestinal polyps is important in unexplained oral cleft patients. To support the clinical management and follow-up of these patients, developing clinical guidelines for the syndrome, whenever

necessary adapted to specific healthcare systems such as those in Europe, are important.

AUTHOR CONTRIBUTIONS

Laura Roht collected and analysed the cohort data, compiled the manuscript. Hanne K. Hyldebrandt, Astrid T. Stormorken, Hilde Nordgarden, Rolf H. Sijmons, Dennis K. Bos, Douglas Riegert-Johnson, Sarah Mantia-Macklin and Kai Muru provided and analysed clinical data of the patients, and reviewed the manuscript. Pilvi Ilves analysed radiological investigations of the patients, and reviewed the manuscript. Monica H. Wojcik analysed genetic data of the patients, and reviewed the manuscript. Tiina Kahre planned and conducted the study and reviewed the manuscript. Katrin Õunap planned and conducted the study and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHIC STATEMENT

The study was performed according to Helsinki's declaration and in accordance with local protocols and regulations of their institutions. The Research Ethics Committee of the University of Tartu has approved this study. In addition, the study was approved by Mayo Clinic's institutional review board. In Norway, patients signed Oslo University Hospital's declaration of consent, which was approved by the data protection officer at Oslo University Hospital.

DATA AVAILABILITY STATEMENT

All analysed data consists of patient's personal data and stored by regulations of the institutions. On request is possible to share anonymised data.

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REFERENCES

Beard, C., Purvis, R., Winship, I. M., Macrae, F. A., & Buchanan, D. D. (2019). Phenotypic confirmation of oligodontia, colorectal polyposis and cancer in a family carrying an exon 7 nonsense variant in the AXIN2 gene. *Familial Cancer*, *18*(3), 311–315. https://doi.org/10.1007/s10689-019-00120-0

Bilgin, N. (2018). Etiology and treatment alternatives in tooth agenesis: A comprehensive review. *Stomatological Disease and Science*, *2*, 9.

Cobourne, M., Xavier, G. M., Depew, M., Hagan, L., Sealby, J., & Webster, Z. (2009). Sonic hedgehog signaling inhibits palatogenesis and arrests tooth development in a mouse model of the nevoid basal cell carcinoma syndrome. *Developmental Biology*, *331*, 38–49.

Frebourg, T., Oliveira, C., Hochain, P., Karam, R., Manouvrier, S., Graziadio, C., Vekemans, M., Hartmann, A., Baert-Desurmont, S., Alexandre, C., Lejeune Dumoulin, S., Marroni, C., Martin, C., Castedo, S., Lovett, M., Winston, J., Machado, J. C., Attié, T., Jabs, E. W., … Seruca, R. (2006). Cleft lip/palate and CDH1/E-cadherin mutations in families with hereditary diffuse gastric cancer. *Journal of Medical Genetics*, *43*(2), 138–142. https://doi.org/10.1136/jmg.2005.031385

Hlouskova, A., Bielik, P., Bonczek, O., Balcar, V. J., & Sery, O. (2017). Mutations in AXIN2 gene as a risk factor for tooth agenesis and cancer: A review. *Neuroendocrinology Letters*, *38*(3), 131–137. Retrieved from <Go to ISI>://WOS:000406690100001.

Jarvinen, E., Shimomura-Kuroki, J., Balic, A., Jussila, M., & Thesleff, I. (2018). Mesenchymal Wnt/beta-catenin signaling limits tooth number. *Development*, *145*(4), dev158048. https://doi.org/10.1242/dev.158048

Lammi, L., Arte, S., Somer, M., Jarvinen, H., Lahermo, P., Thesleff, I., Pirinen, S., & Nieminen, P. (2004). Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. *American Journal of Human Genetics*, *74*(5), 1043–1050. https://doi.org/10.1086/386293

Letra, A., Bjork, B., Cooper, M. E., Szabo-Rogers, H., Deleyiannis, F. W., Field, L. L., Czeizel, A. E., Ma, L., Garlet, G. P., Poletta, F. A., Mereb, J. C., Lopez-Camelo, J. S., Castilla, E. E., Orioli, I. M., Wendell, S., Blanton, S. H., Liu, K., Hecht, J. T., Marazita, M. L., … Silva, R. M. (2012). Association of AXIN2 with non-syndromic oral clefts in multiple populations. *Journal of Dental Research*, *91*(5), 473–478. https://doi.org/10.1177/0022034512440578

Letra, A., Menezes, R., Granjeiro, J. M., & Vieira, A. R. (2009). AXIN2 and CDH1 polymorphisms, tooth agenesis, and oral clefts. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *85*(2), 169–173. https://doi.org/10.1002/bdra.20489

Liu, B., Rooker, S. M., & Helms, J. A. (2010). Molecular control of facial morphology. *Seminars in Cell & Developmental Biology*, *21*(3), 309–313. https://doi.org/10.1016/j.semcdb.2009.09.002

Liu, W. (2000). Mutations in AXIN2 cause colorectal cancer with defective mismatch repair by activating β-catenin/TCF signaling. *Nature Genetics*, *26*, 146–147.

Macklin-Mantia, S. K., Hines, S. L., Chaichana, K. L., Donaldson, A. M., Ko, S. L., Zhai, Q., Samadder, N. J., & Riegert-Johnson,

D. L. (2020). Case report expanding the germline AXIN2- related phenotype to include olfactory neuroblastoma and gastric adenoma. *BMC Medical Genetics*, *21*(1), 161. https://doi.org/10.1186/s12881-020-01103-0

Macklin-Mantia, S. K., & Riegert-Johnson, D. L. (2020). An American patient with polyposis carrying a Scandinavian AXIN2 pathogenic variant. *Hereditary Cancer in Clinical Practice*, *18*, 14. https://doi.org/10.1186/s13053-020-00149-8

Mazzoni, S. M., & Fearon, E. R. (2014). AXIN1 and AXIN2 variants in gastrointestinal cancers. *Cancer Letters*, *355*(1), 1–8. https://doi.org/10.1016/j.canlet.2014.09.018

WEB RESOURCES

Clinvar Database. https://www.ncbi.nlm.nih.gov/clinvar/ (accessed on January, February, and March 2021).

ERN GENTURIS website. https://www.genturis.eu/l=eng/Home.html (accessed on March 2021).

The Human Gene Mutation Database (HGMD). http://www.hgmd.cf.ac.uk/ac/index.php (accessed on January, February, March 2021).

The National Comprehensive Cancer Network (NCCN). https://www.nccn.org/ (accessed on March 2021).

The portal for rare diseases and orphan drugs. https://www.orpha.net/consor/cgibin/OC_Exp.php?lng=EN&Expert=300576 (accessed on September 2020).

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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