Mutations in AXIN2 Cause Familial Tooth Agenesis and Predispose to Colorectal Cancer

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Wnt signaling regulates embryonic pattern formation and morphogenesis of most organs. Aberrations of regulation of Wnt signaling may lead to cancer. Here, we have used positional cloning to identify the causative mutation in a Finnish family in which severe permanent tooth agenesis (oligodontia) and colorectal neoplasia segregate with dominant inheritance. Eleven members of the family lacked at least eight permanent teeth, two of whom developed only three permanent teeth. Colorectal cancer or precancerous lesions of variable types were found in eight of the patients with oligodontia. We show that oligodontia and predisposition to cancer are caused by a nonsense mutation, Arg656Stop, in the Wnt-signaling regulator AXIN2. In addition, we identified a de novo frameshift mutation 1994-1995insG in AXIN2 in an unrelated young patient with severe tooth agenesis. Both mutations are expected to activate Wnt signaling. The results provide the first evidence of the importance of Wnt signaling for the development of dentition in humans and suggest that an intricate control of Wnt-signal activity is necessary for normal tooth development, since both inhibition and stimulation of Wnt signaling may lead to tooth agenesis. Our findings introduce a new gene for hereditary colorectal cancer and suggest that tooth agenesis may be an indicator of cancer susceptibility.

Morphogenesis and tissue regeneration are based on tight control of cell homeostasis. Wnt signaling has been implicated in regulation of diverse developmental events, as well as in aberrations of cell homeostasis that may lead to cancer (Huelsken and Birchmeier 2001; Alonso and Fuchs 2003; Lustig and Behrens 2003; Giles et al. 2003). Central to the mediation of Wnt signals is the regulation of β-catenin level and localization. When cells receive a Wnt signal, β-catenin is stabilized and binds transcription factors of the TCF family regulating expression of Wnt target genes. In the absence of Wnt signal, β-catenin is subjected to phosphorylation and subsequent degradation by action of a multiprotein complex (Seidensticker and Behrens 2000). The complex is organized by APC (product of the adenomatous polyposis coli gene) and Axin1 or its homolog Axin2, which serve as scaffolding components for the complex. Axin1 and Axin2 (also called “conduit” or “axil”) share a similar domain structure with binding sites for β-catenin, GSK3β, APC, and disheveled (Behrens et al. 1998; Yamamoto et al. 1998; Mai et al. 1999; Seidensticker and Behrens 2000). Axin1 is expressed uniformly during development, whereas Axin2 is expressed in a tissue- and stage-specific manner; for example, in somites, branchial arches, and limb buds (Jho et al. 2002; Aulehla et al. 2003). Axin2 is induced by Wnt signaling, suggesting that Axin2 expression serves as a negative-feedback regulator of Wnt signaling (Jho et al. 2002; Leung et al. 2002).

Mutations that facilitate the escape of β-catenin from the action of the degradation complex may lead to cancer due to increased transcription of Wnt target genes. Somatic mutations in β-catenin and molecules of the degradation complex have been found in cancer tissues, including skin, gastrointestinal, ovarian, and hepatocellular tumors (Huelsken and Birchmeier 2001; Giles et al. 2003; Lustig and Behrens 2003). Germine loss-of-function mutations in APC cause familial adenomatous polyposis (FAP [MIM 175100]), comprising ~10% of hereditary colorectal cancer (Groden et al. 1991; Kinzler et al. 1996).
Agenesis of one or more permanent teeth (hypodontia [MIM 106600]) is the most common congenital malformation in humans. More than 20% of the population lacks one or more third molars (wisdom teeth) congenitally, and >5% lack other permanent teeth, most commonly some of the second premolars or upper lateral incisors (Vastardis 2000; Arte 2001). Genetic factors causing these common types of hypodontia have remained unknown. The genetic background for more-severe tooth agenesis, oligodontia (MIM 604625), is better understood. Oligodontia, defined as congenital lack of six or more permanent teeth, third molars excluded, is relatively rare and is most often associated with some multigang syndrome. It has become obvious that both hypodontia and oligodontia are genetically very heterogeneous. It is plausible that mutations or common variants in genes in which loss-of-function mutations cause severe tooth agenesis may significantly contribute also to the background of the common hypodontia. For nonsyndromic oligodontia, dominant mutations in transcription factors MSX1 and PAX9 have been described (Vastardis et al. 1996; Stockton et al. 2000; Nieminen et al. 2001; Lammi et al. 2003). In homozygous Msx1- and Pax9-null mutant mice, tooth development is arrested at an early stage, whereas heterozygotes have normal dentition (Satokata and Maas 1994; Peters et al. 1998). There is experimental evidence indicating that Msx1 and Pax9 are required for the mediation of BMP and FGF signaling, respectively. Experiments in mice have also shown that Shh and Wnt signals are necessary for normal tooth development. It is thought that integrated networks of signaling pathways are the key regulators of tooth morphogenesis (Jernvall and Thesleff 2000; Thesleff 2003).

Here, we describe a Finnish four-generation family in which oligodontia segregated as an autosomal dominant trait (fig. 1A). The proband and her father were orthodontic patients at the Institute of Dentistry, University of Helsinki. The diagnosis of oligodontia was based on clinical examination, panoramic radiographs, and interviews. The study was approved by the Ethics Committee of the Institute of Dentistry, and informed consent was obtained from all participating individuals.

Altogether, 11 family members lacked at least eight permanent teeth, and, in 2 of them, only three permanent teeth had developed (figs. 1B, 1C, and 2). The oligodontia phenotype appeared completely penetrant. The majority of the affected family members lacked most permanent molars, premolars, lower incisors, and upper lateral incisors. Three also lacked all canines. Most often present were upper central incisors (always present), canines, first premolars, and first molars. One affected individual (IV:1) also lacked four deciduous incisors. Other individuals reported no defects in primary dentition, but dental records were not always available. The considerable variation in the number and type of missing teeth is typical for familial oligodontia (Vastardis et al. 1996; Stockton et al. 2000; Lammi et al. 2003; Nieminen et al. 2003). However, the tooth phenotypes in this family...
Agenesis of permanent teeth caused by AXIN2 mutations. The number of missing permanent teeth ranged from 8 to 29. Agenesis of deciduous teeth was found in only one individual (IV:1) (not shown).

were more severe than and different from oligodontia in families with mutations reported elsewhere. MSX1 mutations are associated especially with agenesis of the second premolars and third molars and PAX9 mutations with molar tooth agenesis (Vastardis et al. 1996; Stockton et al. 2000; Nieminen et al. 2001, 2003; Lammi et al. 2003). The phenotype also differed from hypohidrotic ectodermal dysplasia (HED [MIM 305100]), in which both deciduous and permanent teeth are severely affected and the teeth that develop are often conical in shape. Furthermore, the other ectodermal symptoms in nails, hair, or skin typical for HED were not found in our patients.

The patient records initially revealed two patients with oligodontia from the oldest generation (individuals II:2 and II:7) who had a history of colorectal neoplasia (fig. 1A; table 1). During this study, 10 other family members (7 subjects with oligodontia and 3 healthy individuals) were studied through use of colonoscopy or sigmoidoscopy. Colorectal neoplasia was found in six family members with oligodontia (individuals II:4, II:8, III:2, III:4, III:5, and III:7). No signs of neoplasia were found in family members with normal dentition. In the family, risk for colorectal neoplasia thus appeared to be associated with oligodontia. The colorectal findings were variable, since polyposis was found in a few patients, whereas it was not otherwise evident, even in the patients with severe neoplasia (table 1).

Seventeen members of the family were available for molecular analysis. DNA was isolated from venous blood samples with the Puregene DNA purification system (Gentra). Sequencing of the coding regions of the oligodontia candidate genes PAX9 (Nieminen et al. 2001) and MSX1 of the proband and his father did not reveal mutations. For a genomewide search with linkage analysis, tooth agenesis was modeled as an autosomal dominant trait with 95% penetrance and a gene frequency of 0.0001. Linkage analysis excluded loci for PAX9, MSX1, LEF1, and PITX2. Analysis of chromosomes of the patients with colorectal neoplasia excluded also the APC locus. In pairwise analysis with Mlink (Lathrop et al. 1984), highest pairwise LOD scores were obtained in chromosome 17 for two neighboring markers, 3.07 for D17S944 and 3.23 for D17S949. No recombinants were found for those markers and the disease. Genotyping more markers defined a maximal recombination-free region of ~15 cM between markers D17S948 and D17S1352, according to Génétion and Marshfield genetic maps (University of California–Santa Cruz Web site). Multipoint analysis with Simwalk (Sobel and Lange 1996) gave a maximum LOD score of 3.55 between markers D17S1792 and D17S1351 (fig. 3), providing evidence for linkage of oligodontia to a locus in that region.

The region includes ≈80 known or predicted genes. None of these had been previously implicated in tooth agenesis in humans or mice. AXIN2 (MIM 604425) was selected as a candidate gene because it is involved in Wnt signaling and because somatic mutations of AXIN2 have been found in colorectal tumors with defective mismatch repair (Behrens et al. 1998; Liu et al. 2000). Direct sequencing of AXIN2-coding regions and flanking intronic sequences (fig. 4; table A [online only]; Dental Genetics Group Web site) revealed a 1966C→T transition in exon 7, leading to a change of arginine 656 to a stop codon and premature termination of translation (fig. 4A and 4C). Further sequencing revealed the presence of the same nonsense mutation in all family members who had oligodontia but not in the healthy family members or in >100 unrelated control individuals.

While screening the AXIN2 gene for mutations in other patients with oligodontia, we identified a heterozygous 1-bp insertion (fig. 4B), after nucleotide 1994 in exon 7, in a 13-year-old boy with a very similar tooth phenotype as that in the family described above (fig. 2). The
mutation was not found in his healthy parents, indicating that it is a de novo germline mutation in one of the parents. The mutation expands one of the several mononucleotide repeats in exon 7 of AXIN2 and recodes the amino acids starting at Asn666, incorporating a stop codon 40 codons later. This mutation was identical to one of the somatic frameshift mutations described for colorectal cancer tissue (Liu et al. 2000). The finding of this de novo mutation suggests the vulnerability of the mononucleotide repeats in exon 7 of AXIN2 for frameshift mutations also in absence of defective mismatch repair (Liu et al. 2000). The young age of the patient prevents the confirmation of cancer predisposition.

Both mutations introduce a premature stop codon to exon 7 of the AXIN2 gene. According to current knowledge, in-frame stop codons introduced by mutations may lead to degradation of mRNA via the nonsense-mediated mRNA decay mechanism (Wilusz et al. 2001; Cartegni et al. 2002). The mRNAs transcribed from the mutated copies of AXIN2 fulfill the requirement that the premature stop codon be located $\geq$50 bp upstream of the last exon-exon junction, suggesting that the mutated AXIN2 mRNAs are guided to the degradation pathway. A protein product translated from the mutated mRNA would be truncated and lacking the C-terminal domain (fig. 4C and 4D), which, in Axin1, mediates oligomerization and interactions with protein phosphatase 2A, disheveled, and LRP5/6 (Seidensticker and Behrens 2000; Mao et al. 2001). Since the truncations would cause the predicted oligomerization domain to be lost and, in the case of the frameshift mutation, the length of recoded amino acids would be short, a dominant negative effect would be improbable. Stop-codon–creating exon 7 frameshift mutants of AXIN2 are associated with accumulation of $\beta$-catenin in the nucleus of cancer cells and, in transfection experiments, activate a TCF-promoted reporter gene (Liu et al. 2000). C-terminal deletions in mouse Axin1 have been shown to abolish its ability to inhibit Wnt reporter-gene activity (Hsu et al. 1999). These data in-

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**Table 1**

**Colorectal Findings in Family Members**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age* (years)</th>
<th>Colorectal Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>II:1b</td>
<td>60</td>
<td>No abnormal findings in colonoscopy</td>
</tr>
<tr>
<td>II:2</td>
<td>54</td>
<td>A widely metastasized adenocarcinoma originating from the hepatic flexure of the colon</td>
</tr>
<tr>
<td>II:4</td>
<td>62</td>
<td>Two hyperplastic polyps and two tubular adenomas with mild dysplasia (cecum and ascending colon)</td>
</tr>
<tr>
<td>II:7</td>
<td>57</td>
<td>68 adenomatous polyps of different sizes in colon, with severe dysplastic changes</td>
</tr>
<tr>
<td>II:8</td>
<td>38</td>
<td>A tubular adenoma in the rectum and the hepatic flexure of colon showing mild dysplasia</td>
</tr>
<tr>
<td>III:2</td>
<td>35</td>
<td>A 5–6-cm-wide sessile polyposus tumor of the ascending colon, histopathology showing a tubulovillous adenoma with severe dysplasia but no invasive carcinoma</td>
</tr>
<tr>
<td>III:3b</td>
<td>29</td>
<td>2 6-mm polyps removed at colonoscopy (cecum and upper rectum); histology showed hyperplastic polyp mixed with tubular adenoma, mild dysplasia</td>
</tr>
<tr>
<td>III:5</td>
<td>31</td>
<td>27 A sessile hyperplastic polyp of 10 mm in diameter removed at colonoscopy from the ascending colon</td>
</tr>
<tr>
<td>III:6b</td>
<td>36</td>
<td>No abnormal findings in sigmoidoscopy</td>
</tr>
<tr>
<td>III:7</td>
<td>35</td>
<td>10–20 hyperplastic polyps in the ascending colon; a large sessile hyperplastic polyp in cecum; 2 small adenomas in the sigmoid colon</td>
</tr>
<tr>
<td>III:8</td>
<td>26</td>
<td>No abnormal findings in colonoscopy</td>
</tr>
</tbody>
</table>

* Age at the time of examination.
* Patient not affected with oligodontia.
Figure 4  Sequence analysis of AXIN2. Genomic DNA was amplified with Dynazyme Ext (Finnzymes) and primers for exons 1–10 of AXIN2 (table A [online only]; GenBank). PCR products were purified with ExoSAP-IT (USB) and were sequenced with ABI BigDye terminator reagents, version 3.1 (Applied Biosystems). The reactions were analyzed in an ABI 3730 DNA sequencer in Molecular Medicine Sequencing Laboratory, Biomedicum Helsinki. A, Chromatogram from sequencing of exon 7 of the proband (III:8) of the three-generation family. All affected family members had the same heterozygous 1994C–T mutation, indicated by the arrow. The mutation was not present in the unaffected family members. B, Chromatogram from sequencing of exon 7 of the sporadic case of oligodontia (de novo mutation). Arrow indicates the position of a heterozygous insertion of a G after nucleotide 1994. C, Partial amino acid sequence from exon 7 of human AXIN2 and consequences of two mutations. Red indicates the mutation in the family affected with oligodontia. Green indicates the de novo frameshift mutation. The Green “Q” indicates the mutation in the family affected with oligodontia. D, Genomic and protein structure of AXIN2. Boxes represent exons; the predicted interaction domains of AXIN2 protein are depicted with colors. APC = adenomatous polyposis coli; GSK = glycogen synthase kinase 3β; Dsh = disheveled homology domain. ATG denotes the beginning of the coding region; TGA denotes the stop codon.

Figure 5  In situ hybridization analysis of Axin2 and Axin1 expression during mouse tooth development. Serial paraffin sections were cut through paraformaldehyde-fixed heads of embryonic and newborn mice. The in situ hybridization with [35S-UTP (Amersham)–labeled riboprobes spanning 1,234 bp of Axin1 and 1,178 bp of Axin2 sequence from exons 1–4 (GenBank) was performed as described elsewhere (Wilkinson and Green 1990). In situ grains in dark-field images of the slides were painted red and superimposed on corresponding bright field images. A–E, Frontal sections. F, Sagittal section. A–C, E, and F, Axin2. D, Axin1. A, In an E11 embryo, tooth development is initiated. In upper and lower jaws, Axin2 is expressed in the mesenchyme underlying the oral epithelium (arrow). B, At E13, teeth have reached the bud stage. Expression of Axin2 continues in the mesenchyme and is particularly intense adjacent to the tooth buds (arrow). C, In an E14 embryo, teeth are at the cap stage. In addition to the mesenchyme (arrow), expression is seen in the enamel knot (open arrow). D, At E14, Axin1 is expressed weakly and uniformly throughout dental and oral tissues. Similar Axin1 expression was seen at all observed developmental stages (data not shown). E, At E17, tooth development is at the bell stage. Axin2 is expressed in the dental papilla mesenchyme (arrow), as well as in the mesenchymal cells directly underlying all epithelia. F, In a newborn mouse, cell differentiation has started in the molars. Axin2 expression is intense in the layer of mesenchymal odontoblasts and preodontoblasts (open arrow). Intense expression is also seen under the oral epithelium (arrow). oe = oral epithelium; de = dental epithelium; m = mesenchyme; t = tongue; M1 = first molar; M2 = second molar; E = embryonic day.

It has been shown that, in mice, Axin2 exhibits tissue- and stage-specific expression patterns during development (Jho et al. 2002; Aulehla et al. 2003). It is expressed in the primitive streak and later in the dorsal neural tube and developing somites, as well as in the branchial arches and the limb buds of mouse embryos (Jho et al. 2002). In the presomitic mesoderm, it is expressed in an oscillating pattern, and an orchestrating role for Axin2 and Wnt3a was suggested in the establishment of the segmental pattern during somitogenesis (Aulehla et al. 2003). In the developing gut, Axin2 expression was found in the inter villus epithelium (Jho et al. 2002). We studied the expression of Axin1 and Axin2 during mouse tooth development by in situ hybridization. Axin1 was expressed uniformly in the developing jaws (fig. 5D), whereas Axin2 expression was most intense in the mesenchyme underlying the oral and dental epithelium (fig. 5A–5C, 5E, and 5F). At more advanced stages of tooth morphogenesis, the expression was intense in the odontoblasts producing dentine (fig. 5F). Axin2 expression was also seen in the enamel knot (fig. 5C), an epithelial signaling center...
that regulates tooth morphogenesis (Jernvall and Thesleff 2000).

The involvement of Wnt-signaling genes in carcinogenesis is well established, but relatively little is known about the connection between them and congenital malformations in humans. In addition to the neoplastic manifestations caused by loss-of-function mutations of APC, mutations in two Wnt receptors, LRP5 and frizzled-4, are known to affect regulation of bone density or to disturb eye development (Gong et al. 2001; Robitaille et al. 2002; Van Wesenbeck et al. 2003). Initially, most genes that participate in Wnt signaling and especially their developmental roles have been identified on the basis of Drosophila and mouse mutants. The understanding of functions of Axins is based on mouse and zebrafish mutants, which show that Axin1 function is necessary for embryonic axis formation and for normal development of neural tube and heart (Zeng et al. 1997; Heisenberg et al. 2001; van de Water et al. 2001). However, the functions of Axin2 remain to be demonstrated. It is interesting that Axin2 expression is induced by Wnt signaling, suggesting a suppressing role for Axin2 through a negative-feedback loop (Jho et al. 2002; Leung et al. 2002). As a consequence of the AXIN2 mutations described in this study, the feedback regulation would be attenuated.

In this study, we present the first evidence for the functions of AXIN2. The Arg656Stop mutation was present in all 11 patients with oligodontia from a multigeneration family, whereas it was not present in the healthy individuals, thus showing complete segregation with the oligodontia phenotype. The mutation was not found in >200 control chromosomes. Another mutation in AXIN2 was found in an unrelated patient with oligodontia. Furthermore, in situ hybridization showed that, in mice, Axin2 is expressed in developing dental tissues. In conclusion, the mutations of AXIN2 are responsible for the severe oligodontia of the patients, showing that AXIN2 function is essential for the development of dentition in humans. Since the deciduous dentition was unaffected in most patients, it appears that AXIN2 function is especially critical for the development of permanent teeth. Considering the importance of Wnt signaling for the development of most organs, it is surprising that congenital malformations caused by mutations in AXIN2 were found only in the dentition.

In mutant mice, tooth development is inhibited when the Wnt pathway is blocked by inactivating Lef1 function or by overexpressing the Wnt inhibitor Dkk (van Genderen et al. 1994; Andl et al. 2002). On the other hand, occurrence of odontomas and supernumerary teeth has been reported in association with FAP (in this case, called “Gardner syndrome”) (Fitzgerald 1943; Gardner 1962; Ida et al. 1981; Wolf et al. 1986). Even though there is no data available as to whether supernumerary teeth occur in those families in which loss-of-function mutations in APC have been identified, it can be speculated that formation of supernumerary teeth in patients with FAP resulted from overactivation of Wnt signaling. Thus, it appears that disruption of Wnt signaling leads to failure of tooth development, whereas increased signaling leads to development of supernumerary teeth. However, our data indicate that overstimulation of the Wnt pathway may also lead to failure of tooth morphogenesis. Recent data based on a mathematical model for Wnt pathway and its experimental confirmation indicate that Axin and APC promote the formation of β-catenin degradation complexes in very different ways (Lee et al. 2003). The different outcomes of loss-of-function mutations in APC and AXIN2 may also be explained if AXIN2 is especially important as a negative-feedback regulator. It is interesting that Axin2 expression during mouse tooth development coincided with that of the TCF-family member Lef1, although Lef1 is much more intensely expressed in the epithelial signaling center enamel knot than Axin2 (Kratochwil et al. 1996). The function of Lef1 is to activate Wnt target genes, and, in the enamel knot, it is necessary for the bud-to-cap transition during tooth morphogenesis (Kratochwil et al. 1996). Our findings suggest that suppression of Wnt function is necessary during specific stages of tooth development in dental mesenchyme and/or in the enamel knot. This underlines the importance of modulating the intensity of signaling for morphogenetic responses. The central role of specific inhibitors of signal pathways in the regulation of embryonic development has become apparent during recent years. For instance, in embryonic axis formation, inhibition of Wnt and BMP signaling is essential, and differential Wnt activities determine the formation of head, trunk, and tail (Zeng et al. 1997; Kieck and Niehrs 2001).

Our results also provide strong evidence that familial colorectal cancer can be caused by mutations in AXIN2. Colorectal neoplasia in the family described in this study was found only in association with oligodontia and the AXIN2 mutation and affected all those of the oldest generation who had the mutation. The causative role of the AXIN2 mutation is also corroborated by earlier findings of somatic mutations in AXIN2 in tumor tissues (Liu et al. 2000; Wu et al. 2001; Taniguchi et al. 2002). Identification of AXIN2 as a new gene that is responsible for hereditary cancer reduces the remarkable 40% proportion of hereditary colorectal cancers without known molecular causes. It appears that colorectal neoplasia caused by loss of function of AXIN2 has very high or full penetrance. It is interesting that there is a large intrafamilial variation in type and number of colorectal neoplasias and polyps caused by the AXIN2 mutation. The phenotype appears to be distinct from FAP, resem-
bling the attenuated form of FAP (AFAP) described elsewhere (Knudsen et al. 2003).

The AXIN2 Arg656Stop mutation is one of the rare cases in which a mutation simultaneously predisposes to cancer and causes a hypoplastic malformation. Our finding reflects the development of teeth as epithelial appendages regulated by molecular mechanisms similar to those that are involved in colorectal carcinogenesis, thus highlighting commonalities between developmental pathways and tissue homeostasis. It is an intriguing possibility that tooth agenesis may be used as an indicator of susceptibility for colorectal cancer.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/GenBank/ (for human genomic contig NT_010783, mouse Axin1 mRNA [accession number AF009011], and mouse Axin2 mRNA [accession number NM_015732])

Online Mendelian Inheritance in Man (OMIM), http://www .ncbi.nlm.nih.gov/Omim/ (for FAP/Gardner syndrome, hypodontia, oligodontia, HED, and AXIN2)

University of California–Santa Cruz Genome Bioinformatics, http://genome.ucsc.edu/ (for positions in Génèthon and Marshfield genetic maps)

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