The dental phenotype in familial adenomatous polyposis: diagnostic application of a weighted scoring system for changes on dental panoramic radiographs

Nalin Thakker, Rhodri Davies, Keith Horner, John Armstrong, Tara Clancy, Simon Guy, Rodney Harris, Philip Sloan, Gareth Evans

Abstract

A weighted scoring system (Dental Panoramic Radiograph Score) taking into consideration the nature, extent, and site of osseous and dental changes on dental panoramic radiographs in familial adenomatous polyposis is described. The weighting takes into consideration the incidence of the anomaly in the general population. The reliability of the system was tested by application to 85 people known to be affected by clinical or mutation analysis, 30 people lacking mutation in the adenomatous polyposis gene, and 19 people shown to be at low risk (<1%) by linkage analysis. Using the highest thresholds, a specificity of 100% and sensitivity of ≈68% was obtained. If all positive findings were considered as significant, sensitivity was increased to ≈82% but the specificity was reduced to ≈88%. Significant DPRS findings were observed at a significantly higher frequency in patients aged over 20 compared to the patients aged 20 and under. Overall, ≈68% of the affected subjects had significant changes, and ≈18% had normal appearance on DPR, with the remainder having changes classified as minimal or equivocal.


Familial adenomatous polyposis (FAP) is an autosomal dominant condition characterised by the development of multiple adenomatous polyps in the colon and rectum with high risk of subsequent malignant transformation. In addition, extracolonic changes occur in many affected subjects. These include epidermoid cysts, desmoid tumours, congenital hypertrophy of retinal pigment epithelium (CHRPE), osseous changes in the jaws and skeleton, and dental anomalies. FAP results from germine mutations in the adenomatous polyposis coli (APC) gene on chromosome 5q21.12

The adenomatous polyps usually develop in the colon or rectum or both in adolescence or early adulthood and malignant transformation usually occurs between the ages of 30 and 40.1 Early identification of affected subjects and prophylactic surgical intervention is essential in preventing the development of colorectal carcinomas. Furthermore, presymptomatic diagnosis is vital since two-thirds of those presenting with symptoms will have already developed carcinoma and consequently will have a poorer prognosis.45

In families with a history of FAP, subjects at risk may be diagnosed by using genetic markers closely linked to the APC locus1 or by identification of mutations in the APC gene.27 However, linked markers may not always be informative or the pedigree structure may be unsuitable for linkage analysis. Furthermore, most mutations are unique within given families.12 Current mutation screening methods are only able to identify the pathological mutation in 60 to 70% of the families. Alternative mutation analysis strategies involving in vitro transcriptional/translational assays may prove to be more efficient.11 In the absence of suitable rapid genetic tests for some families, there is a dependence on clinical screening of subjects at risk for the identification of those affected. This involves regular colonoscopy. In addition, other extracolonic features, such as CHRPE and changes in the jaws, which may anticipate the appearance of colonic polyps may prove useful phenotypic markers. CHRPE is reported to be present in between 58 and 100% of cases10,13 and the presence or absence of CHRPE has been used in optimal risk estimation in FAP.10,11,12 Numerous studies have also identified jaw changes including osseous lesions, odontomes, supernumerary teeth, and an increased incidence of impacted teeth.11,14–24 The use of these changes in a diagnostic test for FAP has been limited because of the presence of similar changes in unaffected people, lack of data on the reliability of such a test, and lack of familiarity of geneticists with features identified on dental panoramic radiographs. In this paper we describe in detail the radiographic changes in FAP patients. In addition, we describe a weighted scoring system for these changes and report its application and reliability in the diagnosis of FAP.

Subjects and methods

FAP FAMILIES

The families were identified from the North West Regional Polyposis Register, St Mary’s Hospital, Manchester and included patients referred from the regional gastroenterology and surgical units, and the University Dental Hos-
Briefly, the sample included 85 known affected FAP patients (group A: patients who were either known to be affected at the time of examination or were subsequently identified as affected clinically or by mutation analysis) and 30 definitely unaffected people (group B: lacking the mutation present in the APC gene of affected members of their family). Two other groups of “unaffected” people from FAP families were also included: 19 subjects determined by linkage analysis with both intragenic and closely linked flanking markers to be at least 1% risk of FAP (group C) and 19 subjects determined by clinical examination to be at low risk (group D). The latter is defined by the absence of polyps and CHRPE at the age of 25.

**DENTAL PANORAMIC RADIOGRAPH SCORE (DPRS)**

All patients were subjected to clinical, oral, and radiographic examination with informed consent and ethical approval. The radiographic examination consisted of dental panoramic radiography (DPR). Additional appropriate introral radiographs were done where indicated to confirm DPR findings but were not used in data analysis. The radiographs were examined blind and independently by three experienced observers including one consultant dental radiologist. The grading of radiographs, detailed below, was done retrospectively.

The DPR scoring criteria are detailed in table 2. Various anomalies have been identified by us in a pilot study (unpublished data) and by others in previous studies. These were used to derive definitions of criteria for scoring. Well defined, round endosteal (fig 1) or exosteal (fig 2) radiodensities with regular margins were scored as osteomas; well defined radiodensities but with irregularly shaped margins were scored as dense bone islands (DBIs, fig 3), and an ill defined increase in bone density...
was scored as hazy sclerosis (fig 4). The size or the extent of the osseous lesions was also noted. In addition, for hazy sclerosis, association with teeth was recorded. Other features used as diagnostic criteria were presence or absence of odontomes (figs 4 and 5), supernumerary teeth, and unerupted teeth (fig 5). Unerupted third molars were excluded from analysis.

Four possible outcomes were considered; these included (1) lack of any anomalies, (2) minimal change(s), (3) equivocal change(s), and (4) significant change(s). Each DPR anomaly was assigned a score. An overall Dental Panoramic Radiograph Score (DPRS) was determined by summation of the score for individual anomalies. The significance of the findings was determined by assigning a specific range of values of DPRS to each of the four outcomes (table 3).

Where two features of any anomaly were considered in the scores, for example, size and numbers for osteomas and DBIs, all lesions were individually assigned a size score together with a single numbers score. This is illustrated by considering three osteomas of sizes 0·5 cm, 1 cm, and 4·0 cm. The score for the number of osteomas is 9 and the scores for the sizes are 0, 3, and 6, giving a final anomaly score of 18.

The score assigned to each anomaly reflected its level of clinical significance if the anomaly occurred in isolation. If an anomaly in isolation is considered clinically significant then a score at or above the summed significance level (≥ 7) is assigned to it, for example, presence of two osteomas of whatever size. In contrast, for an anomaly not considered to be significant if present in isolation because, for example, it is seen in the general population relatively frequently, a relatively low score was given. Thus, in the absence of other features, the DPRS in this case would not exceed that required to achieve significance. This is illustrated by the scores assigned to the presence of single unerupted teeth or a few DBIs of less than 0·5 cm. The weighting applied to each score is further considered below in the Discussion.

![Figure 3](image3.png) Part of a dental panoramic radiograph showing irregular radiodense lesion typical of a dense bone island (arrow).

![Figure 4](image4.png) Part of a dental panoramic radiograph showing hazy sclerosis affecting the body of the mandible. An odontome is present (arrow).

![Figure 5](image5.png) Area of a dental panoramic radiograph from a patient wearing complete dentures. An unerupted maxillary canine tooth is present (large arrow) in close association with an odontome (small arrow).

**Table 3** Significance of the dental panoramic radiograph scores (DPRS). Calculation of DPRS is detailed in “Subjects and method.”

<table>
<thead>
<tr>
<th>Dental panoramic radiograph score</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>Normal</td>
</tr>
<tr>
<td>3-4</td>
<td>Minimal change(s)</td>
</tr>
<tr>
<td>5-6</td>
<td>Equivocal change(s)</td>
</tr>
<tr>
<td>≥7</td>
<td>Significant change(s)</td>
</tr>
</tbody>
</table>
Table 4  Frequency of anomalies in each group. The number of patients with the anomalies in each group is indicated and percentages are given in parentheses.

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Group A (n=85)</th>
<th>Group B (n=30)</th>
<th>Group C (n=19)</th>
<th>Group D (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomas</td>
<td>46 (54.1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>Dense bone islands</td>
<td>36 (42.4%)</td>
<td>2 (6.7%)</td>
<td>1 (5.3%)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>Hazy sclerosis</td>
<td>28 (33.3%)</td>
<td>1 (3.3%)</td>
<td>2 (10.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Supernumerary teeth</td>
<td>8 (9.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Unerupted teeth</td>
<td>13 (14.1%)</td>
<td>0 (0%)</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 5  Frequency of the possible DPR outcomes in each group. The number of patients with the different DPR findings in each group is indicated and percentages are given in parentheses.

<table>
<thead>
<tr>
<th>DPR outcome</th>
<th>Group A (n=85)</th>
<th>Group B (n=30)</th>
<th>Group C (n=19)</th>
<th>Group D (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>15 (17.7%)</td>
<td>27 (90.0%)</td>
<td>17 (89.5%)</td>
<td>13 (68.5%)</td>
</tr>
<tr>
<td>Equivocal change(s)</td>
<td>3 (3.5%)</td>
<td>0 (0%)</td>
<td>1 (5.3%)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Significant change(s)</td>
<td>58 (60.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (10.5%)</td>
</tr>
</tbody>
</table>

In addition to providing a value of diagnostic significance, the DPRS also provides a measure of severity of the phenotype by including number, size, or extent of changes in the individual scores beyond that necessary to establish outcome in a diagnostic test. This is illustrated by the increasingly higher scores given to increasing number of osteomas seen on DPRS even though two or more osteomas or a single osteoma greater than 0.5 cm would be sufficient for diagnosis of FAP.

STATISTICAL ANALYSIS

Unless stated otherwise, the χ² test with Yates’s correction was used where appropriate to test for statistical significance with the accepted significance level of p<0.05. Where expected values in the χ² test fell below 5, Fisher’s exact probability test was used with the accepted significance level of p<0.05. Bayesian calculations were used to derive probability of carrier status using DPRS outcomes as conditional probability.

RELIABILITY OF TEST

The reliability of the test was determined by application of the DPRS to the known affected (group A) and unaffected groups (groups B and C). The clinically low risk group was excluded from analysis in view of the recently reported non-penetration and delayed onset of polyposis (see Discussion). Various parameters (specificity, sensitivity, false positive rate, false negative rate, positive predictive accuracy, negative predictive accuracy, false alarm rate, and efficiency) were determined.

Results

The percentage of patients in each of the four groups (A–D) showing changes on DPRS is shown in table 4. There were no statistically significant differences (Fisher’s exact probability test) between the frequencies of anomalies observed in the two unaffected groups (B and C); for the purpose of further statistical analysis the groups were combined. The differences between the frequency of DPR anomalies in the FAP affected group (group A) and the unaffected groups (groups B and C) were statistically significant. The commonest anomaly seen in the FAP affected group was bony changes: 81% of patients showed osseous changes including osteomas, DBI, or hazy sclerosis (although not all the changes were individually significant by our criteria). Osseous anomalies were also the commonest change seen in the unaffected groups (B and C) although they were present in only 8% of the members of these groups combined. Of the patients in group A, 12 showed a single significant change; eight patients had osteomas, three patients had DBIs, and one patient had hazy sclerosis. Dental abnormalities (odontomes, supernumerary teeth, and impacted/unerupted teeth) were seen in 37% of the FAP patients. In contrast only one person in group B had a dental anomaly (maxillary supernumerary tooth). Six of the 19 patients (32%) in group D (clinically low risk) had osseous anomalies but none had dental anomalies.

The number of people classified as having significant changes, equivocal changes, minimal changes, and normal radiographic appearance in each group are shown in table 5. The salient features are that in group A, 58 of the 85 subjects showed significant changes compared to 0 out of 30 in group B and 0 out of 19 in group C. Three of 85 patients in group A and one in 49 patients in groups B and C had equivocal changes. When the significant findings were counted as positive and all other categories were classified as negative, there was a statistically significant difference in the frequency of positive and negative test outcomes between the affected group (A) and the unaffected groups (B and C).

Using these counts in Bayesian calculation with a prior probability of 50% of being carrier, the probability of carrier status was approximately 17% with a negative DPRS finding, 54% with minimal or equivocal changes, and 100% (diagnostic) with significant changes.

In the clinically low risk group of 19 people, two showed significant changes, two had equivocal changes, two had minimal changes, and 13 had no changes. The reliability of the test when applied to the known affected group (A) and the known unaffected groups (B and C) is shown in table 6. When the significant findings were counted as positive and all other categories were classified as negative, the test had speci-
ficity and positive predictive accuracy of 100% coupled with a false positive rate and false alarm rate of 0%. The sensitivity of the test was 68.2% with a negative predictive accuracy of 64.5% and a false negative rate of 31.8%. The efficiency of the test was approximately 79%.

The sensitivity of the test was only slightly improved (from 68.2% to 71.8%) by considering the equivocal findings as positive (table 6). However, if minimal changes were also considered as positive then sensitivity increased to 82.4%. The specificity and the positive predictive accuracy were reduced to 87.8% and 92.1% respectively. The efficiency of the test increased to 84.3% (table 6).

In group A, an increasing incidence of significant DPR anomalies (DPRS ≥ 7) with age was observed up to the age of 30 (table 7). Forty two percent of patients aged 20 and under had a DPRS ≥ 7 compared to 75% of the patients over 20. This difference was statistically significant. However, the number of patients at extremes of age was small.

Discussion
The desirability of early identification of people with FAP in the at risk group is apparent because screening for colonic polyps by colonoscopy could be limited to these subjects thus saving those unaffected from unnecessary, unpleasant, and costly investigations. Although dental changes have been described previously in FAP, their use in the diagnosis of FAP has been limited. This is chiefly because of the non-specific nature of some of the changes and the consequent difficulty in attaching any significance to them in individual patients. In order to overcome this problem we have designed a weighted Dental Panoramic Radiograph Score (DPRS) which takes into consideration the nature, extent, and site of the changes seen on a dental panoramic radiograph.

In applying the weighting to each score, we have taken into consideration our clinical experience and previous studies of radiographic anomalies in the general population and in FAP patients. Small radiodensities, with or without regular margins and particularly in the mandibular molar and premolar regions, have been described in between 0% and 10% of the general population. These changes are often seen in relation to the roots of teeth when present and presumably occur in response to pulpal or periodontal pathoses. We have observed three types of osseous lesions in FAP patients: osteomas, dense bone islands, and hazy sclerosis. Previous studies of FAP patients have grouped these as “osteomatos” lesions or radio-opacities. We have chosen to consider these lesions separately because in our experience, small and often multiple radio-opacities with irregular margins (DBIs by our definition) are often seen in unaffected patients. In contrast, solitary osteomas (circular radio-opaque lesions with regular margins) greater than 0.5 cm and multiple osteomas are not seen in such patients. This is confirmed by the absence of osteomas in all the members and the presence of DBIs in three of the 49 (~6%) members of the unaffected groups (B and C) in the present study. These differences are reflected in the weighting given to these entities in the DPRS. Hazy sclerosis in FAP patients has not been previously described. As this appearance may be seen as an inflammatory bone response to periodontal disease in unaffected subjects, an appropriate weighting was given in DPRS to the site and extent of such changes. Overall, hazy sclerosis unrelated to teeth was given a higher score than that associated with teeth.

Supernumerary teeth, in particular those in the maxillary midline (mesiodens), occur in the general population with a frequency of up to 1%. In the absence of other changes, we have given a relatively low score value to the presence of mesiodens and equivocal score value to the presence of any other single supernumerary tooth. Unerupted teeth are relatively common in the general population occurring with an overall frequency of 17%. Unerupted third molars are even more common (frequency of ~22%), so we have disregarded these in the DPRS. However, other unerupted teeth are included although a low score is given to the presence of a single unerupted tooth.

In the present study, all radiographic anomalies were significantly more frequent in the affected group than in the unaffected group. The most frequent observation in the FAP patients was the presence of osseous lesions although we did not consider all of these changes to be individually significant in the DPRS. Our data has been weighted with previous studies which reported osseous changes in between 76 and 93% and dental changes in 30% of FAP patients.

The DPRS is a highly reliable diagnostic index. With a DPRS ≥ 7, the specificity and positive predictive rate was 100%, and a false positive rate of 0% was obtained. However, the sensitivity is relatively low at 69% and this is not improved significantly by consideration of the equivocal DPRS values as significant. This level of sensitivity may appear surprising given the high prevalence of osseous changes in the affected subjects; however, not all of these were deemed to be significant in the scoring of DPRS. Thirteen of the 85 (~15%) FAP patients had what we classified as insignificant osseous changes compared to five of the 49 (~10%) members of the unaffected groups (B and C). The sensitivity is considerably improved if all positive findings, that is, the minimal and equivocal changes, are considered as significant; however, the specificity and the positive predictive accuracy are slightly re-

<table>
<thead>
<tr>
<th>Age range</th>
<th>No of patients with DPRS ≥ 7 (%)</th>
<th>Total No</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20</td>
<td>8 (42.1)</td>
<td>19</td>
</tr>
<tr>
<td>21-30</td>
<td>10 (71.4)</td>
<td>14</td>
</tr>
<tr>
<td>31-40</td>
<td>22 (76.9)</td>
<td>26</td>
</tr>
<tr>
<td>41-50</td>
<td>8 (66.7)</td>
<td>12</td>
</tr>
<tr>
<td>51-60</td>
<td>10 (71.4)</td>
<td>14</td>
</tr>
</tbody>
</table>
duced. Overall, the efficiency of the test is slightly improved (from \(~ 79\% \text{ to } \sim 84\%)\). These data are remarkably similar to the previously reported sensitivity and specificity of 82\% and 90\% respectively for findings characteristic of FAP on DPRSs. \(^{20}\) Giardiello et al\(^{10}\) also reported a similar level of sensitivity (84\%) but a much lower specificity (50\%). However, they considered the presence of one or more jaw lesions (any well circumscribed area of radio-opacity or an odontome) as significant. This is clearly different from the thresholds used in the present study. The presence of six osseomas has been reported to be diagnostic for FAP\(^{11}\) but patients with such changes only represent a small percentage of the total sample.

In comparison, the other most commonly used extracranial phenotype marker, CHRPE, is reported to have sensitivity of between 58 and 100\% using various diagnostic threshold criteria. \(^{10-13}\) In unaffected populations, CHRPE is reported in up to 43\% of people. \(^{11}\) A high level of specificity (between 94 and 100\%) is also reported applying diagnostic thresholds based on type, size, or number of CHRPE lesions or presence of bilateral lesions. \(^{11-13}\) Depending on the thresholds applied in the DPRSs (as discussed above), comparable levels of specificity and sensitivity are obtained in the present study.

Application of DPRS to the clinically low risk group (group D) showed two subjects with a significant score. They were aged 58 and 52, were free of colonic polyps, and did not have CHRPE. One had a single osseoma \(< 1\text{ cm}\) and the other had an osseoma \((\sim 7 \text{ mm})\) and a small dense bone island \((\sim 5 \text{ mm})\) respectively. Previously reported incidence data indicate that at risk people with no retinal features and negative colono-scopy at the age of 34 years should be considered to be free of FAP. This suggests that the two patients with the significant DPRS scores in the clinically low risk group represent false positives in our test. However, we have recently described four families with non-penetrance and late onset of polyposis. \(^{14}\) Our studies indicate that at least 5\% of affected subjects will be free of polyps on significant colono-scopy at 30 years of age and some still have no polyps in their fifties. Thus the two subjects may represent atypical FAP cases particularly in view of the high specificity of the test determined in this study. Mutation analysis is continuing and should establish which of these possibilities is correct.

The higher frequency of significant DPRS findings in the patients aged over 20 compared to the patients aged 20 and under suggests that there may be an age dependent appearance of the jaw changes. This indicates that the test is more likely to be informative in the older group of patients.

The usefulness of DPR in the diagnosis of FAP is apparent from the data presented here. DPRS provides a highly specific method of determining significance of findings on DPR. In addition, the incidence data should permit use of DPR findings together with ophthalmoscopy findings and linkage analysis in Bayesian calculations for optimal assessments of risk where mutation analysis is not feasible. The DPRS is a highly reliable and reproducible index in our hands; however, we have examined a large series of patients to date and have considerable experience in the assessment of the radiographs. Further independent assessment of DPRS by other groups is necessary in determining the usefulness or otherwise of the test.

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