Genetic Mutations in Certain Head and Neck Conditions of Interest to the Dentist

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Abstract

This article identifies certain syndromes of the head and neck, which a dentist may see in clinical practice, and relates these syndromes to their sites of mutation on involved genes. This paper is timely with the near completion of the Human Genome Project, the mapping of the entire human genetic material. Knowing the site of the genetic lesion is important in helping clinicians understand the genetic basis for these conditions, and may help in our future understanding of remedies and treatments.

MeSH Key Words: *craniofacial abnormalities/genetics; human; genome; mutation*

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The basis of many diseases is the accidental alteration of DNA. Genetic mutations, or alterations in an individual's genome, can be inherited, affecting cells that perpetually divide (germ-line mutations), or they can occur at any point during a person's life (somatic mutations). Certain mutations exert a wide spectrum of effects, ranging from absence or alteration of protein or tissue factor synthesis to structural changes. To understand these alterations, an understanding of the intact genetic code is required. The most widely known and important attempt to decipher the human genetic code has been the Human Genome Project (www.nhgri.nih.gov).

This is a publicly funded effort to map the human genome in its molecular detail.[1] This ambitious project initially had a planned completion date of 2003. By April 2000, Human Genome Project director Francis Collins estimated that 2-thirds of the human genetic code had been sequenced.[2] However, interest in the project has grown to such a degree that the private company Celera Genomics is now competing with the Human Genome Project in the race to map the genome. Celera claimed in 2001 that it had decoded 99% of human genes.[3] The stakes are high and include the patenting of human genetic information, which is especially important for the pharmaceutical industry.[2]

The full scope of human genetic information is immense. The human genome contains approximately 3 billion nucleotides, making up about 100,000 alleles, which in turn are contained on 46 chromosomes. Transcription of these chromosomes releases the information necessary to synthesize some 6000 proteins. These proteins make up the trillion cells giving rise to the nearly 4000 anatomical structures that constitute a single human being.[4] Mutation, the accidental alteration of the genome, may result in heritable conditions or syndromes affecting any aspect of growth and development.

Inherited syndromes discussed here are some of the anomalies that a practising dentist may encounter. In addition to describing each syndrome, this article discusses known genetic inheritance and causative mutations. Some of the syndromes have additional clinical or radiographic features, but only selected head and neck anomalies are discussed here. **Table 1** summarizes the syndromes under consideration. This area is developing rapidly, and the current body of knowledge is expected to expand and change quickly.

Hypoplastic Amelogenesis Imperfecta

Hypoplastic amelogenesis imperfecta is characterized by

Table 1 Hereditary syndromes of interest to the dentist

Disorder	Inheritance	Locus or loci of mutation
Hypoplastic amelogenesis imperfecta	X-linked dominant	Possible deletion at a locus on Xp22 loci
Cleidocranial dysplasia	Autosomal dominant	Possible deletion at 6p21 or 8q22, or translocation at t(6;18)(p12;q18)
Cleft lip with or without cleft palate	Multifactorial, autosomal recessive or autosomal dominant	Possibly associated with translocation or deletion of 6p region; TGF*alpha* locus may have a role
Dentinogenesis imperfecta	Autosomal dominant	Possible mutation at 4q13–q21
Osteopetrosis	Primarily autosomal recessive, with mild autosomal dominance in some cases	In mice, possible mutation of gene for macrophage colony-stimulating factor; in humans, locus unknown
Mandibulofacial dysostosis	Autosomal dominant	Possible balanced translocation in 5q32–33.2 area
Hypodontia	Multifactorial	Unknown
Nevoid basal cell carcinoma syndrome	Autosomal dominant	9p22.3, smoothened, patched, and sonic hedgehog gene
Crouzons syndrome	Autosomal dominant	Possible missense mutation of FGFR2 gene

TGF*alpha* = transforming growth factor alpha
FGFR2 = fibroblast growth factor

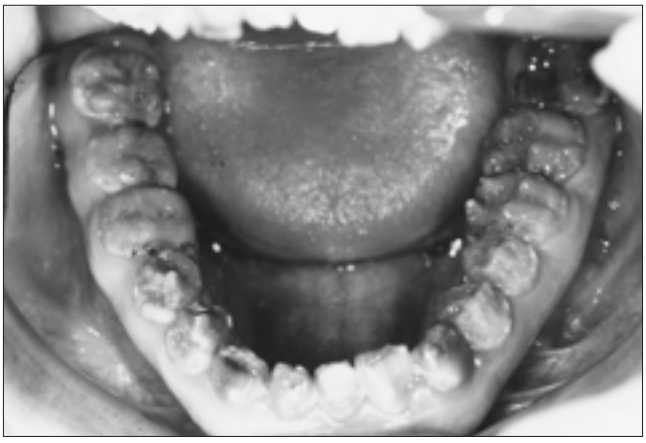

Figure 1: *Hypoplastic amelogenesis imperfecta. Clinical photograph shows irregular enamel formation and severe attrition.*

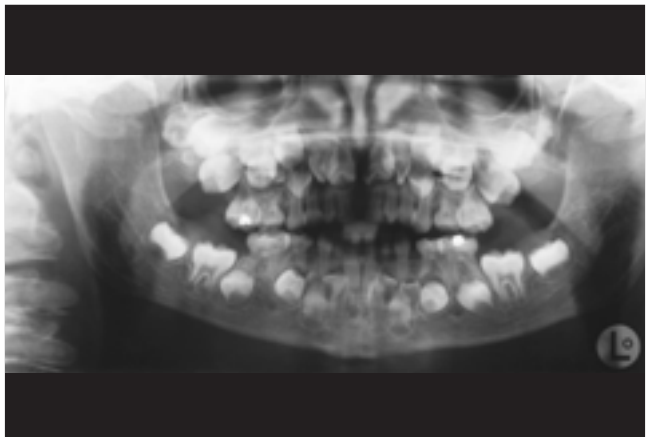

Figure 2: *Cleidocranial dysplasia. Panoramic radiograph shows multiple supernumerary teeth and retained deciduous teeth.*

enamel that is very hard but abnormally thin and irregular, giving rise to the microdontic appearance of affected teeth (**Fig. 1**). In most cases of amelogenesis imperfecta, the condition is inherited as an autosomal dominant trait, but the hypoplastic type is inherited as an X-linked dominant trait.[5] Differences in manifestations between males and females in the hypoplastic forms may be based on the Lyon phenomenon,[6] in which each cell of a female randomly inactivates one or another of the genes on its X chromosome. Affected males may have a very thin, smooth enamel layer, whereas females may have thicker enamel with vertical grooves. The protein defect is thought to affect amelogenin, which is involved in enamel mineralization. Lau and others,[7] using DNA from human–mouse hybrid cells, found the locus for hypoplastic amelogenesis imperfecta on the distal portion of the short (p) arm of the X chromosome. Refining the location further, the locus has been assigned to Xp22.3–p22.1.[8] Lagerstrom and others[9] demonstrated a deletion in the amelogenin gene extending over a 5-kilobase area. Lagerstrom-Fermer and others[10] discovered that the deletion removed 5 of 7 exons. Additional studies have also indicated deletions of various sizes involving the X chromosome.

Cleidocranial Dysplasia

Cleidocranial dysplasia, previously known as cleidocranial dysostosis, includes features such as brachycephaly, frontal bossing, a metopic suture groove, hypoplasia or aplasia of the

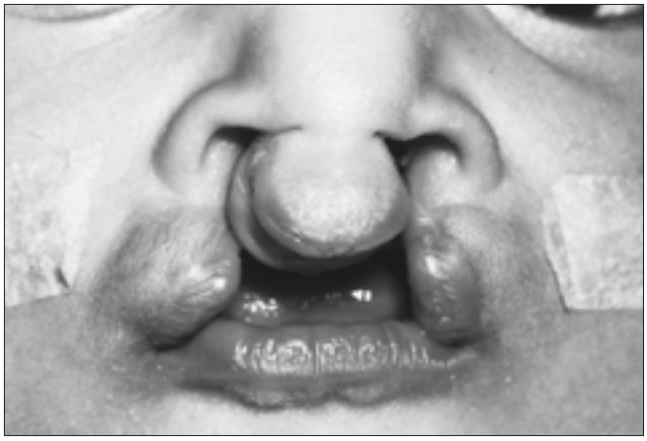

Figure 3: *Bilateral cleft lip and cleft palate.*

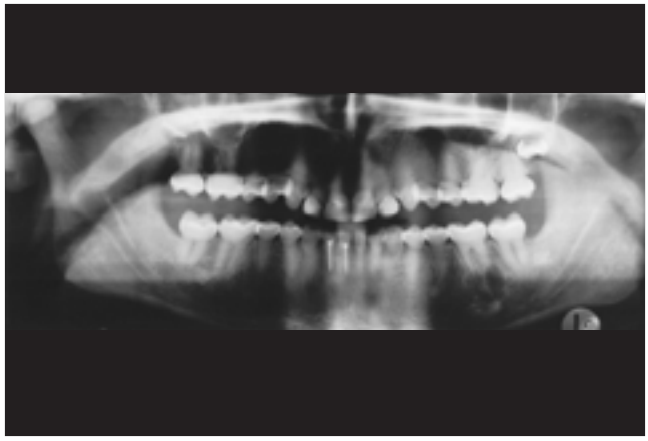

Figure 4: *Dentinogenesis imperfecta. Panoramic radiograph shows obliteration of pulp and periapical abscess of tooth 36.*

clavicles permitting abnormal approximation of the shoulders, delayed exfoliation of the deciduous teeth, delayed eruption of the permanent teeth, ectopic tooth position, and multiple supplemental and supernumerary teeth (**Fig. 2**).

Cleidocranial dysplasia is inherited as an autosomal dominant condition. In 1992, Brueton and others[11] described 3 individuals who had characteristics of this condition and rearrangements of chromosome 8, at locus 8q22. Later, Nienhaus and others[12] reported that the defect causing cleidocranial dysplasia may be located somewhere on chromosome 6. Mundlos and others[13] independently tried to map the mutation assumed to be on the short arm of chromosome 6 and found 4 loci in a region of 6p. For one locus there was a deletion in all affected family members, and the cleidocranial dysplasia gene was therefore assigned to location 6p21. However, the possibility of another locus on a different chromosome has not been excluded. For example, Narahara and others[14] observed cleidocranial dysplasia in association with a translocation involving chromosomes 6 and 18 (**Table 1**).

Nonsyndromic Cleft Lip with or Without Cleft Palate

Nonsyndromic cleft lip with or without cleft palate (**Fig. 3**) appears to be associated with complex genetic changes. Carter and others[15] concluded on the basis of a multigenerational study that the most plausible explanation was the multifactorial threshold model and that a single mutant gene was unlikely. Chung and others[16] performed a comparative gene analysis for cleft lip with and without cleft palate in 2 populations, one Danish and the other Japanese. They concluded that the Danish data were best explained by a combination of major gene actions, which seemed to involve recessive multifactorial inheritance, whereas the Japanese data were best accounted for by the multifactorial threshold model.

Ardinger and others[17] observed an association between 2 restriction fragment length polymorphisms (RFLPs) and the disease, and propose that they could be used as marker loci. The association involved a locus for the transforming growth factor *alpha* (TGF*alpha*) and another for the occurrence of clefting, suggesting that the TGF*alpha* gene or locus in close proximity to it was associated with the condition in certain cases. Chenevix-Trench and others[18] confirmed excess frequency of the TaqI allele. Holder and others[19] also found a significant association between the TaqI RFLP and the occurrence of clefting. Extending their analysis, Chenevix-Trench and others[20] found a significant association between the TGF*alpha* and BamHI restrictions.

Eiberg and others[21] concluded that a major locus for nonsyndromic cleft lip with or without cleft palate was located on the distal portion of the short arm of chromosome 6 as an autosomal dominant form. However, Hecht and others[22] found no evidence of a clefting locus in a region spanning 54 centimorgans of 6p in the families studied by Eiberg and others.[21] Hecht and others[23] described families with multigenerational involvement of cleft lip with or without cleft palate. Reanalysis of the data by Mitchell and Risch[24] revealed that the inheritance was compatible with either a multifactorial threshold model or a model specifying multiple interacting loci.

Davies and others[25] investigated 3 unrelated patients with cleft lip and cleft palate who showed abnormalities of 6p. In 2 patients they found translocation and in the third a deletion, suggesting the existence of a locus for orofacial clefting in the 6p region. Finally, after reviewing the genetic and exogenous factors in the causation of facial clefts, Murray[26] concluded that the strongest evidence implies a primary gene on 6p, with the TGF*alpha* locus acting as a modifier of the clefting state.

Dentinogenesis Imperfecta

Dentinogenesis imperfecta is an entity clearly distinct from osteogenesis imperfecta with opalescent teeth.

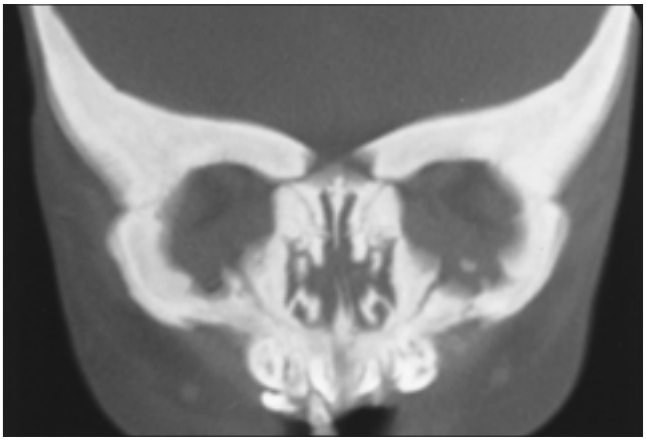

Figure 5: *Osteopetrosis. Computed tomography (bone window) of the head and neck shows increased density of bone, obliteration of marrow spaces and increased thickness of cortical bone.*

Figure 6: *Mandibulofacial dysostosis.*

Dentinogenesis imperfecta affects only the teeth, with no associated increase in fractures of the long bones. The teeth are blue–grey or amber–brown and opalescent. Radiographically, the roots are narrow with little or no evidence of a pulp chamber or canal (**Fig. 4**). The crowns are bulbous with a wide emergence profile. The enamel may split readily from the dentin when subjected to occlusal or other forces.

There are 3 types of dentinogenesis imperfecta. Type I is associated with osteogenesis imperfecta. Type II was previously found to be linked to altered glycosaminoglycan concentrations.[27] Among patients with type II dentinogenesis imperfecta, it was noted that dentin soluble in the calcium chelator ethylenediaminetetra-acetic acid (EDTA) had significantly higher concentrations of glycosaminoglycan than was the case among patients without the condition. Type III is the brandywine form, named for the city Brandywine, Maryland, where there was a large population of patients with this disorder. Type III tends to be less severe than type II.

Dentinogenesis imperfecta has an autosomal dominant pattern of inheritance. Roulston and others[28] found cosegregation between this condition and localized juvenile periodontitis in certain families, which indicated that the loci were separate but perhaps closely linked. Using the genetic mapping technique known as chromosome walking and the study already described,[28] it was concluded that the type I locus is located on chromosome 4, at position q13–q21.[28] A deficiency of dentin phosphoprotein was suggested as a causative factor, given that the locus for this protein was postulated to be near the dentinogenesis imperfecta gene. However, MacDougall and others[29] discovered that the gene for dentin phosphoprotein is not located on chromosome 4, excluding it as a candidate. Osteopontin, a bone glycoprotein, is also expressed in dentin. However, Crosby and others[30] showed no association between a type of polymorphism at the osteopontin locus and type II dentinogenesis imperfecta.

Osteopetrosis

Osteopetrosis (also known as marble bone disease or Albers-Schonberg disease) is characterized by excessive formation of dense trabecular bone and calcified cartilage, especially in the long bones, which leads to obliteration of the marrow spaces (**Fig. 5**). The resulting anemia is accompanied by myeloid metaplasia and hepatosplenomegaly. Patients experience progressive deafness and blindness due to pressure on the cranial nerves at their exiting foramina. Osteopetrosis results from defective resorption of immature bones, because the osteoclasts are hypofunctional or absent.

The inheritance of osteopetrosis is mainly autosomal recessive, although there are mild autosomal dominant forms. For mice with osteopetrosis, Yoshida and others[31] demonstrated that the defect resides in the gene for macrophage colony-stimulating factor (GM-CSF1). In this organism, the condition cannot be cured by transplantation of normal bone marrow cells, which suggests that the defect consists of an abnormal hematopoietic microenvironment rather than an intrinsic defect in progenitors or mature macrophages and osteoclasts. Yoshida and others[31] found insertion of a single base pair in the coding region that generated a stop codon, 21 base pairs from the GM-CSF1 gene. However, it has not yet been proven that a mutation in the GM-CSF1 gene is responsible for osteopetrosis in humans. In this regard, Orchard and others[32] found that the serum of 13 patients with malignant osteopetrosis showed radioimmunoassay levels of GM-CSF1 equal to or greater than the levels in 6 control patients.

Coccia and others[33] performed bone marrow transplants from an unaffected sibling to another sibling with malignant osteopetrosis. In the infant with the condition, the disease was greatly ameliorated when Y-bearing osteoclasts

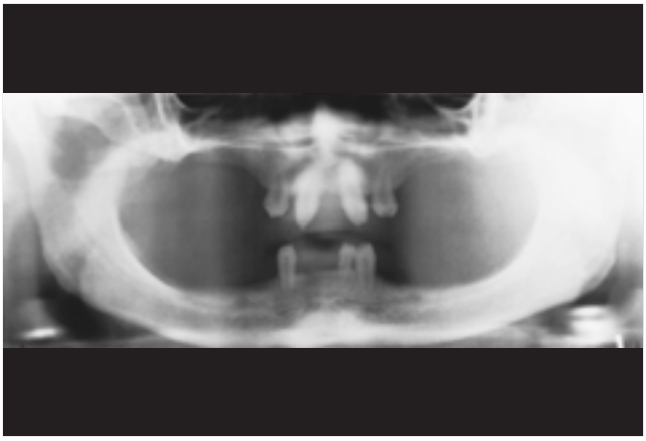

Figure 7: *Oligodontia, imaged with panoramic radiography.*

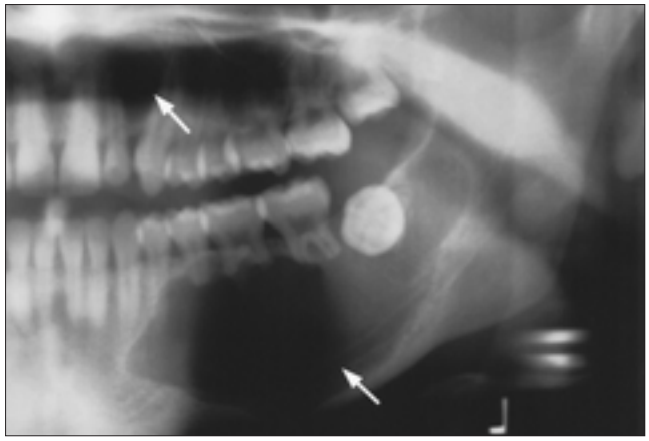

Figure 8: *Nevoid basal cell carcinoma syndrome. Panoramic radiograph shows multiple jaw cysts (white arrows), in particular one in the maxilla between teeth 22 and 23 and another in the body and ascending ramus of the mandible, causing downward displacement of the inferior alveolar nerve and resorption of the roots of permanent teeth 34, 35, 36 and 37. The third permanent molar (tooth 38) is transversely impacted.*

were transferred, and monocyte-macrophage function, previously defective, was restored.

Mandibulofacial Dysostosis

Mandibulofacial dysostosis, also known as Treacher Collins syndrome or Treacher Collins-Franceschetti syndrome, presents with antimongoloid slant of the eyes, coloboma of the lower eyelids, cleft palate, micrognathia, microtia and other deformities of the ears, hypoplasia of the zygomatic arches and macrostomia (**Fig. 6**).

Mandibulofacial dysostosis is inherited as an autosomal dominant trait, which may vary in severity. The allele for the condition is also known as the Treacle gene. Balestrazzi and others[34] described this disorder in a girl with a de novo balanced translocation involving chromosomes 5 and 13 — t(5;13)(p11;q11) — and decreased hexosaminidase B. Hexosaminidase B has its locus HEXB at the 5q13 position. The suggestion that the balanced translocation results in mandibulofacial dysostosis was based on the observed decrease in hexosaminidase B. Dixon and others[35] identified a family with this condition who had a balanced translocation involving chromosomes 6 and 16 — t(6;16)(p21.31;p13.11). These findings later led to linkage of the mandibulofacial dysostosis locus to a balanced translocation of certain markers in the region of 5q31–q34, and further refinement of the location to 5q32–33.2. Jabs and others[36] found a patient with a de novo chromosomal deletion in the region of 4p14–p15.32 with severe manifestations of mandibulofacial dysostosis. These results were corroborated independently by Edery and others.[37]

Hypodontia

Hypodontia is a condition in which the affected individual develops fewer than the normal complement of teeth. In oligodontia, a severe form of hypodontia, at least 6 permanent teeth, excluding the third molars, do not develop (**Fig. 7**). Few dental conditions have been studied more extensively than hypodontia. To a geneticist, hypodontia represents one of the most widespread abnormalities in humans. To an orthodontist, it presents as malocclusion. To an archaeologist, it represents an anomaly that can link 2 or more fossil remains.

Most investigators have considered hypodontia the result of a single dominant gene.[38] However, Suarez and Spence[39] showed, through 2 multiple threshold models, that hypodontia data fit a polygenic model better than a single major gene model. It is now well accepted that the mode of inheritance for hypodontia is polygenic, that is, it is caused by both environmental and genetic factors.

In a study by Eidelman and others,[40] 21,384 children ages 12 to 18 were examined for general signs of hypodontia and then specifically for hypodontia of the maxillary lateral incisors, the second premolars and the mandibular incisors. The prevalence of any type of hypodontia in the general population was 4.61%, and there was no significant difference between males and females in the sample. The prevalence of absence of the maxillary lateral incisors was 2.11% overall and was significantly lower in males than females. The prevalence of absence of the second premolars was 1.87% for the general population, with no significant difference between males and females. The prevalence of absence of the mandibular incisors was 0.68% in the general population and was significantly higher in males than in females (**Table 2**).

In a study, by the same researchers,[41] of families of 305 probands with diagnosed hypodontia, 14.8% of siblings and 9.4% of parents of probands with hypodontia also expressed the condition. More females than males were

Table 2 **Prevalence of oligodontia**

	Prevalence	
Teeth missing	**In general population[40]**	**In first-degree relatives of probands[41]**
Maxillary lateral incisor(s)	2.11% (2.32% of females, 1.89% of males)	10.3% (11.3% of siblings, 9.7% of parents)
Mandibular incisor(s)	0.68% (0.48% of females, 0.89% of males)	9.2% (14.3% of siblings, 5.6% of parents)

affected. The authors concluded that 11.8% of first-degree relatives of probands with hypodontia showed hypodontia of the same teeth (**Table 2**).

These data show significant differences between the sexes and among the family members of probands. It is therefore possible that differences in the type of hypodontia may be caused by, or associated with, different gene loci or genetic factors. The gene responsible for oligodontia or hypodontia has not yet been located.

Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome, also known as Gorlin-Goltz syndrome, is an autosomal dominant condition characterized by multiple basal cell carcinomas of the skin and other tumours, including medulloblastoma, rhabdomyosarcoma, ovarian fibroma and meningiomas. Affected individuals experience a number of structural malformations, including pitting of the palms and soles, spine and rib abnormalities, ectopic calcifications and midline brain malformations, and they have characteristic coarse facies with frontal bossing.[42] This syndrome (**Figs. 8** and **9**) is also characterized by the development of odontogenic keratocysts of the jaws, often multiple.[43] This presentation contrasts with sporadic odontogenic keratocysts occurring outside the syndrome, which are more likely to be solitary.

The clinical features of nevoid basal cell carcinoma syndrome have long suggested that the underlying genetic disorder is a mutation in a tumour suppressor gene. In other syndromes involving an inherited mutation in a tumour suppressor gene, cancer also occurs at a very early age. For example, Li-Fraumeni syndrome is due to an inherited mutation in the tumour suppressor gene p53 and is characterized by early onset of multiple neoplasias.[44] People with nevoid basal cell carcinoma syndrome exhibit basal cell carcinomas at a far younger age than those with sporadic basal cell carcinomas of the skin; this difference supports the concept that a germ-line mutation in a tumour suppressor gene is the cause of the syndrome.[45]

The causative gene was first identified by positional cloning, which defined the minimum region of deletion on

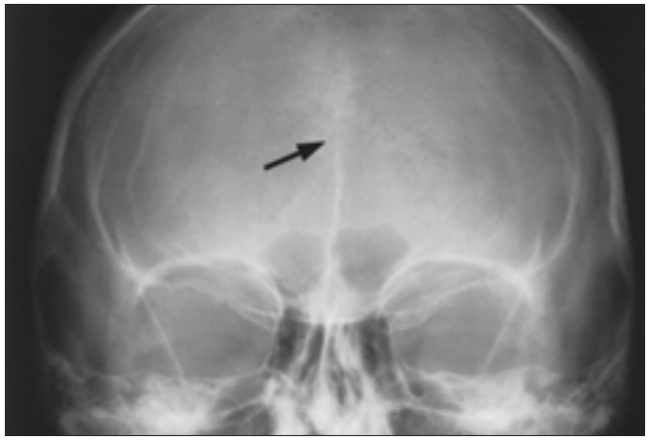

Figure 9: *Nevoid basal cell carcinoma syndrome. Posteroanterior cephalogram shows calcification of the falx cerebri (black arrow).*

chromosome 9 as 9p22.3, where the gene was likely to reside.[46] Subsequent isolation and characterization of the gene showed that it was homologous to the *Drosophila* gene called patched (*PTCH*), which is essential for early embryonic development.[47-49] In *Drosophila*, the protein product of the *PTCH* gene is a component of the hedgehog signalling pathway. The *PTCH* gene actually represses the activity of the hedgehog protein, a protein that acts on a number of other genes including the protein product of the smoothened gene. In humans this pathway is similar, with the *PTCH* gene normally acting to repress the activity of the human homologue of the hedgehog gene, termed the sonic hedgehog gene. Studies in mice have shown that if the *PTCH* gene is not functioning, there is overexpression of the smoothened gene, which leads to increased proliferation of several embryonic cell types. Furthermore, overexpression of either the sonic hedgehog or the smoothened gene has the same net effect as loss or mutation of the repressor gene *PTCH*.[50,51]

Studies in humans have shown that mutations of the *PTCH* gene are involved in the development of basal cell carcinomas in the syndrome. Furthermore, mutations of this gene are also present in a proportion of sporadic basal cell carcinomas, further strong evidence for the crucial role of *PTCH* as a tumour suppressor in human keratinocytes.[52]

Despite compelling evidence that *PTCH* gene mutations are the cause of the abnormalities seen in nevoid basal cell carcinoma syndrome, few studies have directly examined its role in odontogenic keratocysts. Lench and others[53] identified novel mutations of the *PTCH* gene in families who exhibited multiple odontogenic keratocysts. Interestingly, the importance of the *PTCH* gene in the development of sporadic (nonsyndromic) keratocysts has been supported by the finding of gene loss in the 9p22.3 region in DNA extracted from biopsy samples of these cysts.[54]

Conclusions

Our knowledge of the loci of many genetic mutations is rapidly increasing. For example, mutation of the fibroblast growth factor gene has recently been implicated in Crouzons syndrome.[55] Localization of defects within the genome is an essential step in understanding and possibly correcting genetic disorders. Once the locations are known, therapeutic changes may be possible through specific identification of causative sites.

Gene therapy and genetic engineering are still in their earliest phases, and there are many hurdles to overcome. Characteristics common to the disorders that have been discussed here include their low prevalence and the complexity of accurately locating the defective gene.

Although great strides continue to be made, most work has been on animal models, and there are still many gaps in human genetic knowledge. Of significant concern are the ethical ramifications of permanently altering an individual's genetic makeup. For the future, many techniques in nanotechnology[56,57] remain to be perfected and, at a philosophical level, many issues remain to be debated and reconciled. ➧

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CDA Resource Centre

The Resource Centre can provide MEDLINE searches and copies of articles on any of the syndromes discussed in this article. CDA members can contact the Resource Centre at tel.: 1-800-267-6354 or (613) 523-1770, ext. 2223; fax: (613) 523-6574; e-mail: info@cda-adc.ca.