ABSTRACT

Dental development is part of the craniofacial organogenesis, starting from the pluripotent cephalic neural crest cells, continuing with their movement towards the first pharyngeal arch and leading to the development of many elements of the craniofacial structures. Tooth developmental disorders can be caused by genetic abnormalities at any level of the genomic information (chromosomal, monogenic, polygenic-multifactorial). Dentin genetic abnormalities have been known for several years and include two entities: dentinogenesis imperfecta (DI) and dentin dysplasia (DD). Osteogenesis imperfecta (OI) (also known as brittle bone disease) is a connective tissue disorder (collagen disorders) characterized by bone fragility leading to recurrent bone fractures and in the severe forms to bone deformities and shortening. 12 clearly described types of OI and 2 other OI phenotypical entities have been described until present, the best known being due to various COL1A1 and COL1A2 mutations, (genes which encode for the collagen type I pro-alpha 1 and 2 polypeptide chains). Although DI is part of the clinical features reported in OI, not all types of OI have dentin genetic anomalies. For patients with OI, it is extremely important that the clinician understands the possible dental implications associated with the disease. Children with OI should be examined as soon as teeth are erupted to prevent loss of tooth structure and seen frequently to restore any new enamel fracture and maintain their oral health. Genetic testing is available in single-gene or multigene panel analysis and is essential in the diagnosis and in defining the type of OI or DI of each patient.

Keywords: dentinogenesis, osteogenesis, gene panel

It is a well-known fact the numerous genetic factors are involved in tooth morphogenesis, with a continuously rising number of associated candidate genes and variants.

Dental development is part of the craniofacial organogenesis, starting from the pluripotent cephalic neural crest cells, continuing with their movement towards the first pharyngeal arch and leading to the development of many elements of the craniofacial structures (1-3).

Tooth developmental disorders can be caused by genetic abnormalities (at any level of the genomic information (chromosomal, monogenic, polygenic-multifactorial) (3,4). They have been reported either as isolated defects or part of the symptomatology of various complex multisystemic genetic syndromes (4).

Numerous classifications have been made in respect of dental anomalies, depending on tooth shape, number, size, structure, formation, a.o. (5,7).

Certain genetic and biological defects as are the embryonic origins of dental cells, dentition patterns, morpho- and histogenesis, the specific location of tooth development, tooth identity, final differentiation of odontoblasts and ameloblasts, synthesis and mineralization of the dentine and...
enamel matrix, development of the root and periodontium, eruption of teeth are linked to these classifications (6-9).

Dental anomalies and defects are a consequence of mistakes during any of these complex processes. The involvement of the environment in gene functioning is well documented and represent, along with the human genome, and essential factor in defining certain acquired dental anomalies (2,10,11).

Important progress has been made regarding biological pathways associated with dentin matrix formation and tooth disease (12,13).

Dentin genetic abnormalities have been known for several years and include two entities: dentinogenesis imperfecta (DI) and dentin dysplasia (DD) (2,4). The estimated incidence of DI is between 1/6,000 and 1/8,000 and approx. 1/100 000 for dentin dysplasia (1).

Dentinogenesis imperfecta is an autosomal dominant disease characterized by severe hypomineralization of dentin and altered dentin structure and has been classified into three types (11).

Shields type I DI is associated with osteogenesis imperfecta that affects the connective tissues resulting in dentin dysplasia and is caused by mutations in the COL1A1 gene (collagen, type 1, Alpha-1) located on chromosome 17q and COL1A2 gene on chromosome 7q (11,14).

Shields type II DI (OMIM 125490) is caused by pathogenic mutations in the DSPP gene (dentin sialophosphoprotein, OMIM 125485), located at 4q22.1. It is identical clinically, radiologically, and histologically to type 1, but without being associated to osteogenesis imperfecta (1,14,15).

Shields type III DI (OMIM 125500) is a rare form of DI involving, unlike types 1 and 2, teeth with shell-like appearance and multiple pulp exposures. Mutations in the DSPP gene have also been reported to be causative for this DI type (1,14).

Osteogenesis imperfecta (OI) (also known as brittle bone disease) is a connective tissue disorder

### Table 1. Types of osteogenesis imperfecta with / without dentinogenesis imperfecta

| Type of OI | Inheritance pattern | Disease OMIM No. | Severity | With / without DI | Causative gene | OMIM No. | Location |
|------------|---------------------|------------------|----------|------------------|----------------|----------|----------|
| I          | AD                  | 166200           | Mild     | DI - rare        | COL1A1        | 120150   | 17q21.33 |
| II         | AD                  | 166210           | Lethal   | No DI            | COL1A1 COL1A2 | 120150 120160 | 17q21.33 7q21.3 |
| III        | AD                  | 259420           | Severe (deforming) | DI - both primary and secondary teeth | COL1A1 COL1A2 | 120160 | 7q21.3 |
| IV         | AD                  | 166220           | Moderate | DI present       | COL1A1 COL1A2 | 120160 | 7q21.3 |
| V          | AD                  | 610967           | Highly variable (even among carriers of the same mutation) | DI - rare | IFITM5 | 614757 | 11p15.5 |
| VI         | AR                  | 613982           | Severe (‘fish scale’ lamellae at iliac biopsy) | No DI | SERPINF1 | 172860 | 17p13.3 |
| VII        | AR                  | 610682           | Extremely severe - lethal | No DI | CRTAP | 605497 | 3p22.3 |
| VIII       | AR                  | 610915           | Severe - lethal (no DI) | No DI | P3H1 (LEPRE1) | 610339 | 1p34.2 |
| IX         | AR                  | 259440           | Moderate - severe | No DI | PPIB | 123841 | 15q22.31 |
| X          | AR                  | 613848           | Severe | DI reported in some patients | SERPINH1 | 600943 | 11q13.5 |
| XI/ BRKS1  | AR                  | 610968           | Moderate - severe (also Bruck syndrome 1) | DI reported in some patients | FKB10 | 607063 | 17q21.2 |
| XII        | AR                  | 613849           | Moderate - severe | No DI | SP7 | 606633 | 12q 13.13 |
| BRKS2      | AR                  | 609220           | Moderate - severe Bruck syndrome 2 | No reports on DI | PLOD2 | 601865 | 3q24 |
| OPPG       | AR                  | 259770           | Ocular OI (osteoporosis pseudoglioma syndrome) | No reports on DI | LRP5 | 603506 | 11q13.2 |
(collagen disorders) characterized by bone fragility leading to recurrent bone fractures and in the severe forms to bone deformities and shortening (15-18). The incidence of OI is 6-20 / 100,000 newborns, with a 4-10 / 100,000 prevalence rate (2,3).

12 clearly described types of OI and 2 other OI phenotypical entities have been described until present, the best known being due to various COL1A1 and COL1A2 mutations, (genes which encode for the collagen type I pro-alpha 1 and 2 polypeptide chains) (Table 1) (4,14,19,20).

Although DI is part of the clinical features reported in OI, not all types of OI have dentin genetic anomalies (Table 1) (4,14,21).

DIAGNOSIS

Because of the numerous and severe skeletal and dental abnormalities occurring with OI, dental treatment is challenging for both patient and dentist. Being informed about the complexity of the dental treatment for these children will help the dentist in the management of each specific case (5,8,21,22).

The diagnosis of dentinogenesis imperfecta is set through clinical examination that is consistent with the signs of the phenotype. A dental X-ray is important in diagnosing dentinogenesis imperfecta. The specific signs found in a clinical exam may differ depending on the type of dentinogenesis imperfecta (1,6,22).

CONCLUSIONS

Odentogenesis imperfecta is a genetic collagen disorder with dentinogenesis imperfecta as its dental counterpart.

For patients with OI, it is extremely important that the clinician understands the possible dental implications associated with the disease. Children with OI should be examined as soon as teeth are erupted to prevent loss of tooth structure and seen frequently to restore any new enamel fracture and maintain their oral health.

Genetic testing is available in single-gene or multigene panel analysis and is essential in the diagnosis and in defining the type of odontogenesis imperfecta or dentinogenesis imperfecta of each patient.

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