Oral and Craniofacial Clinical Signs Associated to Genetic Conditions in Human Identification Part I: A Review
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Abstract:
Background: Forensic dentistry is one of the most reliable methods used in human identification when other technique as fingerprint, DNA, visual identification cannot be used. Genetic disorders have several manifestations that can target the intra-oral cavity, the cranio-facial area or any location in the human body.

Materials and Methods: A literature search of the scientific database (Medline and Science Direct) for the years 1990 to 2014 was carried out to find out all the available papers that indicate oral, cranio-facial signs, genetic and human identification.

Results: A table with 10 genetic conditions was described with oral and cranio-facial signs that can help forensic specialist in human identification.

Conclusion: This review showed a correlation between genetics, facial and intra-oral signs that would help forensic ondontologist in the identification procedures.

Key Words: Craniofacial, forensic dentistry, genetic, human identification signs

Introduction
Forensic odontology involves the management, examination, evaluation, and presentation of dental evidence in criminal or civil proceeding.1

Forensic dentistry is mainly involved in the identification of deceased individuals.2 Recognition of unknown bodies is associated to their facial appearance, when severe damage occurred to the face; palm and fingerprints are used for identification.3,4 When physical identification and fingerprints cannot be used, dental identification remains one of the most reliable and frequently applied methods of identification, predominantly by comparisons of ante-mortem and post-mortem records.5

The most common methods of identification include visual identification, fingerprinting, serologic and DNA comparison, and anthropologic examination of bone. Each method has its advantages and disadvantages. They all rely on the principle that identification is derived from a positive correlation between known information about a person and findings from a physical examination of the decedent.2

In the last few years, technology has provided new instruments for the three-dimensional analysis of human facial morphology. Currently, quantitative assessments of dimensions, spatial positions, and relative proportions of distinctive facial features can be obtained for both soft- and hard- (skeletal and dental) tissues. Several methods of denture labeling were reported in order to identify edentulous persons.6-8

Genetics is a very important reference that is used in accurate identification of persons; genetic disorders have several manifestations that can target the intra-oral cavity, the craniofacial area, or any location in the human body.9,10

The aim of this paper was to evaluate the association of the oral and craniofacial clinical signs observed in human identification procedure with specific genetic condition.

Materials and Methods
A search of the scientific database (Medline and Science Direct) for the years 1990 to 2014 was performed. Abstract, case report, clinical research, and review articles were included. Keywords used were genetic, forensic, identification, oral, craniofacial, manifestations, and dentistry.

Due to the very broad disorders/clinical signs associated with genetic conditions, a focus on the most frequent reported condition was selected (Table 1).

Oral-facial-digital syndrome
Oro-facial-digital syndrome type I (OFD I) or orofaciiodigital dysostosis. The gene responsible for the syndrome is found
on the short arm of the X chromosome (Xp22.3-p22.2) and mutation analysis has identified the gene as CXORF5, which was later renamed OFD I as the gene responsible for this disorder. The prevalence of OFD I vary in the literature reports. It is estimated to be between 1 out of 50,000 and 1 out of 250,000 live births; it appears to affect all races and ethnicities in equal numbers. Almost all affected individuals are females, as male fetuses with the syndrome die before birth. The craniofacial features of this syndrome include frontal bossing, facial asymmetry, aplasia of alar cartilage, ocular hypertelorism, strabismus, down slanting palpebral fissures, broadened nasal bridge/root, cleft lip/palate, high arched palate, ankyloglossia, oligodontia, supernumerary teeth, hyperplastic frenula, and micrognathia.

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**Table 1: Different intraoral and facial signs associated with genetic conditions.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene involved</th>
<th>Intra-oral signs</th>
<th>Extra-oral signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral-facial-digital syndrome Type I</td>
<td>CXORF5 (OFD I)</td>
<td>High arched palate</td>
<td>Frontal bossing</td>
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<td></td>
<td></td>
<td>Oligodontia</td>
<td>Facial asymmetry</td>
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<td>Supernumerary teeth</td>
<td>Ocular hypertelorism</td>
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<td>Micrognathia</td>
<td>Cleft lip/palate</td>
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<td></td>
<td>Strabismus</td>
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<tr>
<td>Trisomy 13 or Patau syndrome</td>
<td>Chromosome 13 (15q deletion)</td>
<td>Dental caries</td>
<td>Microphthalmia</td>
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<td></td>
<td></td>
<td>Enamel hypoplasia</td>
<td>Strabismus</td>
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<td>Malocclusion</td>
<td>Iris coloboma</td>
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<td></td>
<td></td>
<td>Heavy calculus</td>
<td>Cleft lip/palate</td>
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<td>Decreased salivation</td>
<td>Depressed nasal bridge</td>
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<td></td>
<td>Gingivitis</td>
<td>Stubby nose</td>
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<tr>
<td>Trisomy 21 or Down syndrome</td>
<td>Chromosome 21</td>
<td>Hypodontia</td>
<td>Brachycephaly/flat occipit</td>
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<tr>
<td></td>
<td></td>
<td>Periodontal disease</td>
<td>Upward slanting palpebral fissures/epicanthal folds</td>
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<td>Missing teeth</td>
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<td>Taurodontism</td>
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<td></td>
<td>Malocclusion</td>
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<tr>
<td>Turner syndrome</td>
<td>45X karyotype</td>
<td>Distal molar occlusion</td>
<td>Decreased maxillary growth</td>
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<td></td>
<td></td>
<td>Narrow upper arch</td>
<td>Midface hypoplasia</td>
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<td></td>
<td>Wide lower arch</td>
<td>Wide micrognathic mandible</td>
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<td></td>
<td></td>
<td>Lateral crossbite</td>
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<tr>
<td></td>
<td></td>
<td>Teeth are smaller than normal</td>
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<tr>
<td>Klinefelter syndrome</td>
<td>Extra X or Y chromosome to 47, XXY</td>
<td>Dysmorphic</td>
<td>Hypoplastic teeth</td>
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<td></td>
<td></td>
<td>Hypodontia</td>
<td>Tooth crown larger</td>
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<td></td>
<td>Prognathism</td>
<td>Shovel shaped lateral incisors</td>
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<td>Short filings</td>
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<tr>
<td>Marfan syndrome</td>
<td>FBN1 gene</td>
<td>Stretch marks as pink, white or red streaks in the skin</td>
<td>Crowded teeth</td>
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<td></td>
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<td>Small lower jaw</td>
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<td></td>
<td>High arched palate</td>
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<td></td>
<td></td>
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<td>Dental caries and periodontal diseases</td>
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<tr>
<td>Axenfeld-Rieger syndrome</td>
<td>Mutations in PITX2 on ch 4q25, FOXC1 on 6p25, PAX6 on 11p13, and FOXO1A on 13q14</td>
<td>Glaucoma</td>
<td>Dental hypoplasia</td>
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<td>Craniofacial anomalies</td>
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<tr>
<td>Pycnodysostosis (the Toulouse-Lautrec syndrome)</td>
<td>Cathepsin K gene</td>
<td>Craniofacial anomalies</td>
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<td>Short head</td>
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<tr>
<td>Apert syndrome</td>
<td>Mutation Of FGFR2</td>
<td>Flat occiput</td>
<td>Arched palate with bilateral swellings of the palatine processes</td>
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<td></td>
<td></td>
<td>Short, broad nose with bulbous tip</td>
<td>Ectopic eruption and malocclusion</td>
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<td></td>
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<td>Brachycephaly</td>
<td>Severe crowding</td>
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<td>Midface hypoplasia</td>
<td>Delayed eruption</td>
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<td>Hypotonic lips</td>
<td>Thick gingiva</td>
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<td>Genetically missing teeth</td>
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<td>Anterior open bite</td>
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<td>Bilateral posterior cross-bite</td>
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<tr>
<td>Crouzon syndrome</td>
<td>Chromosome 10q25-10q26</td>
<td>High and large forehead</td>
<td>Class III occlusion</td>
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<td></td>
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<td>Flattening of the occipital region</td>
<td>Maxillary dental arch in V shape</td>
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<td>Maxillary hypoplasia</td>
<td>Spaced teeth</td>
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<td>Exorbitism with hypertelorism</td>
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<td></td>
<td></td>
<td>Maxillary hypoplasia with mandibular prognathism</td>
<td>Congenital cleft in the palate</td>
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</tbody>
</table>
children may have dry, brittle hair, patches of hair loss and whiteheads, followed by the onset of kidney disease in adult.

**Trisomy 13 or Patau syndrome**

The classical features of Patau syndrome or trisomy 13 are defects of the auricles, eyes (microphthalmia, iris coloboma, strabismus, etc.), and mouth (cleft lip, palate or both), holoprosencephaly sequence (including arhinencephaly, cebocephaly, and others), hemangiomas, polydactyly, hyperconvex fingernails, scalp defects, and heart defects. Partial duplications for proximal segments (13q11-ql4) alone show some features of Patau syndrome: including strabismus, depressed nasal bridge, stubby nose, cleft lip/palate, clinodactyly, increased polymorphonuclear projections on the segmented neutrophils, and persistence of Hb F.

**Trisomy 21 (T21) or Down syndrome**

T21 or Down syndrome is the most frequent genetic disorder associated with intellectual disability, affecting between 1.0 and 2.2 of every 1000 live births according to statistics on prenatal testing and selective abortion. Because this chromosomal disorder is also associated with various health problems (e.g. hypotonia, congenital heart defects, gastrointestinal diseases) and distinctive physical stigmata (e.g. round face, epicanthal fold, oblique lid axis, flat nasal bridge), persons with T21 are at high risk of being rejected socially.

**Turner syndrome**

Turner syndrome is a common genetic disorder that has been classically associated with a 45X karyotype, although several other X-chromosomal abnormalities have been identified in these patients, many of which involve mosaicism. It occurs in one out of every 2500 to 3000 female births and is associated with a broad array of potential abnormalities, most of them thought to be caused by haploinsufficiency of genes that are normally expressed by both X chromosomes. Major clinical manifestations include: growth failure, congenital heart defects, gastrointestinal diseases and distinctive physical stigmata (e.g. round face, epicanthal fold, oblique lid axis, flat nasal bridge), persons with T21 are at high risk of being rejected socially.

**Klinefelter syndrome (KS)**

KS describes a sex chromosomal aneuploidy caused by the addition of at least one extra X chromosome to normal male karyotype, XY. It is the most common disorder of sex chromosomes with a prevalence of one in 600 males. Variants of KS are characterized by the addition of an extra X or Y chromosome to classic karyotype 47,XXX. Although somatic malformations and mental retardation are more severe in these variants, most cases remain undiagnosed till puberty when the symptoms of androgen deficiency are recognized. The KS patients present with dysmorphic features consisting of hypodentia, hypoplastic teeth, prognathism, short filtrum, gynecomastia, clinodactyly, and fusiform shaped fingers.

**Marfan syndrome (MFS)**

MFS is an autosomal disease of the connective tissue that is characterized by skeletal anomalies and arachnodactyly. Classic MFS occurs due to a mutation in the FBN1 gene, which codifies for the matrix protein fibrillin, although it is documented that 25% of the sporadic cases lead to de novo mutations in zones, which are distant, several base pairs from this gene sequence. MFS is often diagnosed in association with other disorders of the connective tissue, such as the Loeps-Dietz syndrome and the Shprintzen-Goldberg syndrome.

The skeletal anomalies are the easiest signs to see as flat feet, deep-set eyes, long thin arms, and legs; have loose and flexible joints, tall and slim. MFS can cause the spine to become curved causing backache. Many people with MFS will have some type of vision problem including, myopia, glaucoma, cataracts. However, oral manifestations, such as dental caries and periodontal diseases, although they are common in the general population, also have an increased incidence in patients with the MFS.

**Axenfeld-Rieger syndrome (ARS)**

ARS is a clinically and genetically heterogeneous disorder with an autosomal dominant mode of transmission and great intrafamilial variability, consisting of a family of developmental diseases including anterior segment abnormalities and a variety of systemic manifestations.

ARS can be classified as Axenfeld anomaly (limited to peripheral anterior segment defects), Rieger anomaly (peripheral abnormalities with additional changes in the iris), and Rieger syndrome (ocular anomalies and extraocular developmental defects especially of the teeth, facial bones, and periumbilical skin). Because of the marked genotypic and phenotypic overlap, it has been proposed that these diseases are best considered under the single ARS heading.
These three variations are now recognized as a spectrum of the same syndrome. In the literature, cases with ocular and extraocular manifestations are either defined as ARS or Rieger syndrome.

The most important ocular feature of the ARS is glaucoma, which develops in about 50% of affected individuals. The ocular anomalies are suggested to represent an arrest of tissues derived from neural crest cells in gestation.

In ARS, classical signs represented by dental hypoplasia, craniofacial anomalies, and involuted periumbilical skin can be associated with a wide diversity of other traits, such as limb anomalies, short stature, pituitary anomalies, empty sella syndrome, and a variety of neurological, and dermatological disorders.

**Pycnodysostosis** (the **Toulouse-Lautrec syndrome**)

Pycnodysostosis is a rare autosomal-recessive disorder of osteoclast dysfunction due to mutation of cathepsin K gene causing osteosclerosis. The disease shows equal sex distribution with high parental consanguinity, having an incidence of 1.7 per 1 million births. This disorder is characterized by short stature, increased bone density, short and stubby fingers, fragile bones that may fracture easily, and craniofacial abnormalities caused by delayed suture closure. Patients usually present with frequent fractures even after minor trauma.

**Apert syndrome**

Apert syndrome (Mendelian inheritance in man #101200) represents approximately 5% of all craniosynostosis syndromes. This disorder is characterized by severe craniosynostosis, craniofacial abnormalities, and symmetric syndactyly of the hands and feet. Among the craniofacial alterations are the brachycephaly, midface hypoplasia, flat occiput, hypertelorism, protrusion and a short, broad nose with a bulbous tip. The configuration of the palate is characterized by an arched palate with bilateral swellings of the palatal processes, resulting in a pseudo-cleft in the midline. Other frequent oral findings include hypotonic lips, bifid uvula, delayed or ectopic eruption, and malocclusion. The oral cavity is characterized by impaction, severe crowding, delayed eruption, thick gingiva, sometimes supernumerary teeth, or genetically missing teeth. Other frequent oral cavity findings include Class III malocclusion, anterior open bite, bilateral posterior cross-bite and unilateral posterior crossbite, but to a lesser degree and a midline deviation.

**Crouzon syndrome** (CS)

CS is an autosomal dominant genetic disease with an incidence of 1 in 25,000 births. The mutation in the genes that codify receptor two of the fibroblast growth factor 2, which is mapped to chromosome locus 10q25-10q26 is responsible for the deformities observed.

Extraoral manifestations include a high and large forehead, with the convexity in the region of the anterior fontanelle, flattening of the occipital region and maxillary hypoplasia which are responsible for the appearance of the patient. The clinical features have wide phenotypic variability and consist of bicoronal craniosynostosis, exorbitism with hypertelorism, maxillary hypoplasia with mandibular prognathism, and normal intelligence.

Intraoral features include Class III occlusion and maxillary dental arch in V shape with spaced teeth, congenital cleft in the palate.

**Conclusion and Significance**

Within this search-review, 10 genetic conditions were described with oral and craniofacial signs that can help forensic specialist in human identification. The first part showed a correlation between genetics, facial signs, and intra-oral signs that would help forensic odontologist in the identification procedures. A second part is underwriting that will evaluate the relation between genetic conditions, oral/craniofacial, and general clinical signs.

**References**