“Genetics Request” from the ASE President 2013-2014

What ASE orthodontists “must” (?) know about genetics

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Introduction

Orthodontists know of old that many dentofacial traits - also called dentofacial phenotypes including malocclusions - “run in families”. Through twin research it has become clear that most of the dentofacial traits or phenotypes have a multifactorial etiology, meaning that (small mostly common) variations (called single-nucleotide polymorphisms, or SNPs\(^1\)) in many genes and probably also variations in epigenetic and environmental factors, contribute to the variation in these traits.

In contrast to traits which are determined by the variation (mostly rare mutations) in 1 gene (monogenic traits/disorders, also called Mendelian disorders), the inheritance of multifactorial phenotypes is complex, and do not follow the “simple Mendelian” inheritance patterns/rules (see also added PPT presentation).

Despite the majority of the dentofacial phenotype variation is of multifactorial origin, there still are many distinct dentofacial traits and conditions which have been shown to be monogenic or Mendelian. Most syndromes\(^2\) of head and neck are monogenic conditions (Hennekam et al, 2010\(^3\)), being either inherited from (an) affected or carrier parent(s), or de novo in the individual. The Mendelian patterns include autosomal dominant and recessive inheritance, as well as X-linked (dominant or recessive) inheritance.

The most convenient way to estimate or predict whether a certain trait or condition is determined by variation in 1 gene, is to take a closer look at the occurrence of the trait in the family of the patient. This can best be done by constructing a pedigree of the family and to look at the transmission of the trait of interest – hopefully - through many generations. In the attached PPT-presentation as well as the first weblink (Genetics Home Reference\(^4\)) more details about the characteristics of different Mendelian pedigrees can be checked.

In the section “Conditions”\(^5\) of the Genetics Home Reference website most of the well-known (craniofacial) syndromes like Van der Woude syndrome (Cleft Lip with or without cleft Palate (CL/P) and lip pits), Treacher Collins syndrome, Cleido-Cranial Dysostosis (CCD) and EEC (Ectrodactyly, Ectodermal dysplasia and Cleft ) syndrome, but which will only rarely be seen in the private orthodontic practice, are not only listed, but all useful and updated information concerning these phenotypes are discussed. They are listed per major system involvement (e.g. Bones, Muscles, and connective tissues, Brain and nervous system, Ear, nose, throat, Endocrine system, Eyes and Vision, etc.) but there are 2 subdivisions which are of particular direct interest to orthodontists in their daily patient care, and these are the Mouth and Teeth section as well as the Skin, Hair, and Nails section. It is remarkable that the nr 1 of the most often viewed subtypes includes 3 dental & facial traits, 2 of which have to do with Teeth, i.e. ocular depression, Rieger anomaly and teething delay.

\(^1\) The definition of SNP: single-nucleotide polymorphism (pronounced snip; plural snips) is a DNA sequence variation occurring when a single nucleotide — A, T, C or G — in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes in a human (Wikipedia).

\(^2\) The definition of a syndrome is the combined appearance of different features caused by a common etiological pathogenic gene variant.


\(^4\) http://ghr.nlm.nih.gov/

\(^5\) http://ghr.nlm.nih.gov/BrowseConditions
The epidermal section - Skin, Hair, and Nails, where obviously the teeth could be included as they also are Epidermal Appendages like hair and nails - contains 582 different (syndromic and non-syndromic) phenotypes, in which tooth conditions are often included. When the OMIM (Online Mendelian Inheritance In Man) database and its online genetic searching tool is used with the term Hypodontia, 111 different phenotypes are listed each with a separate OMIM entry. Many of them constitute a subphenotype of one of the many different Ectodermal Dysplasia (ED) syndromes which patients themselves might not yet be aware of, as they can be present in very mild forms, and of which only the teeth might come to their concern.

The role of the orthodontist

From all the non-syndromic craniofacial and dentofacial abnormalities as well as from the syndromes of head and neck, the private orthodontist will most often see either the ED-related or associated forms as well as the non-syndromic orofacial clefts. Of both congenital abnormalities their appearance can be very mild and variable, but they can also be associated with abnormalities in other tissues of ectodermal origin, which can readily be examined and evaluated by the orthodontist as no full physical and medical examination of the patient is necessary. The latter is mostly not the case for associated anomalies from mesodermal or endodermal origin.

The directly related tissues of ectodermal origin include the skin, and the ectodermal appendages like the teeth, the nails, the hair and the glands (sweat, saliva, etc…) . Therefore the orthodontist should pay more attention to these features when examining and interrogating patients with congenitally missing teeth and/or small hypoplastic teeth who are seeking orthodontic treatment in their practices.

Moreover it is easier to collect anamnestic data on the presence of similar orofacial and ectodermal features in the patients family when putting this information into a pedigree, than on data concerning other major health conditions. Besides the missing teeth, questions should be posed on related to ED-features: eventual skin problems, dysplastic nails, problems with sweating, feeling of dry mouth etc.

and should immediately put into the pedigree of the patients family (see PPT presentation for examples).

After completion of the pedigree with the dentofacial phenotype of the patient linked to other family members, a simple general question on “any other health concerns in the family” could be brought up. If there is a clear association between eventual serious health problems like e.g. colorectal or skin

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(pre)malignancies and the dentofacial symptoms in the pedigree, then these issues should be raised to
the patients general physician, who could decide upon a referral to the clinical geneticist or not.

For the exploration of the eventual genetic cause of the patients phenotype, the orthodontist can –
according to her/his own interest - consult different databases, which are publically available (see e.g.
the website of Genetic Home Reference11, or Online Mendelian Inheritance in Man (OMIM)
database12 and GeneCards13), and which can eventually also be shown to the patient, at the time of
the presentation of the treatment plan. Depending on the severity of the possible impact on the health
of the patient and his/her family, the orthodontist can eventually also contact either the general
physician of the patient or a clinical geneticist for an interdisciplinary (telephone)consultation. During
this interdisciplinary consultation, a referral of the patient to the clinical geneticist for genetic
counseling can be considered. After this counseling the clinical geneticist can eventually advise the
patient and eventual other affected family members, to undergo a routine surveillance in the specific
discipline f.e. every year or so. If this is the conclusion reached during the preparatory phase of the
orthodontic treatment planning, this issue can be raised during the proposal of the treatment plan by
the orthodontist.

In the PPT presentation, the Home Page of 3 interesting websites is introduced, ie of the Genetics
Home Reference, OMIM and of GeneCards, each putting a specific emphasis. Also an example is
given for each of them how they can be used as an online tool by the interested orthodontist and also
her/his patients.

If the orthodontist is looking in OMIM for a diagnosis with the term “hypodontia”14, he/she can check
which of these different phenotypes matches best with the one diagnosed in the patient. If none of
them does, it could be a “new”- so far unknown - phenotype, which was at least not reported before
the last update of the OMIM site. Note that the date of the last update is always mentioned for each
OMIM disorder/condition. This explains why at a later access date the “new” phenotype could be
submitted and its etiology eventually be solved by the submitter.

It is good to realize that the expression of the different features composing the phenotypes, can vary.
This variability of expression15 means that all associated features of a particular phenotype - like a
specific type of ED syndrome - are not necessarily present to the same extent in different affected
individuals of one family, despite the fact that all affected family members carry the same gene
mutation. The variation in the rest of the genome probably contributes to the variability of expression
among affected individuals of 1 or of different families carrying exactly the same mutation.

Moreover incomplete penetrance (see footnote 13) can occur, which means that despite the presence of
the pathogenic mutation in an (obligate) carrier of the mutation (check in the pedigree), this member of
the family does not show the phenotype (or only in extremely mild forms). This is good to know as it
can give rise to confusion when interpreting the transmission of the phenotypes through the pedigrees.
Among other reasons, this is why it is of utmost importance to scrutinize the patient for very subtle
characteristics pointing to the phenotype.

13 GeneCards Home Page: http://www.genecards.org/
15 See Tutorial at Home Page of Genetics Home Reference in the Section of Handbook or Glossary
Recently, also solitary (see footnote 13) - diagnosed as non-syndromic - phenotypes have been discovered which were associated with a mutation in 1 gene, often the same gene for which the syndromic form of a certain condition was already found.

Some of these tooth phenotypes, like oligodontia, are genetically heterogeneous (see footnote 13), meaning that mutations in different genes can cause the same or at least similar phenotypes. For hypodontia or oligodontia for example, so far no clear genotype-phenotype correlation is found. There could be, but the number of solved cases so far might still be not big enough.

In conclusion

Despite the rapidly increasing knowledge on the genetic and epigenetic etiology of dentofacial and craniofacial phenotypes, there still is a long way to go before we will fully understand the mechanisms behind the developing phenotypes we are observing in our patients (including severe orthodontic problems) and before we will be able to anticipate or prevent some undesirable or pathological developments (for example by means of novel tools and technologies like pharmacogenomics 16).

Until that day, also orthodontists have a responsibility in observing and diagnosing dentofacial features sometimes associated with underlying and more severe medical problems, that eventually can be passed on to the next generation (like for example the Single Median Maxillary Incisor17 syndrome).

We all have to learn how to deal with such observations which are so far not included in the orthodontic training programs. A closer cooperation between departments of orthodontics and clinical genetics can therefore be helpful. This will pave the way to further interdisciplinary collaboration also in private orthodontic practice, to the benefit of our patients.

16 Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms. Pharmacogenomics may permit drugs to be tailor-made for individuals and adapted to each person’s own genetic makeup. Understanding an individual’s genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety.