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INVITED SPEAKER PRESENTATIONS

I1 Why do experts on ectodermal dysplasia (ED) meet again?
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Head & Face Medicine 2012, 8(Suppl 1):I1

Hypohidrotic ectodermal dysplasia was first described in the mid 19th century by John Thurnam. In 1875, Charles Darwin described the signs and symptoms in a four-generation family, ‘the ten men from Scinde’, explaining X-linked inheritance at the same time when Gregor Mendel mapped the laws of inheritance. The typical clinical expression in boys with X-linked hypohidrotic ED makes this syndrome easy to recognize, although usually not in the newborn, where the vulnerability for overheating is at its peak. Still a majority of these boys seems to be diagnosed by dentists, either when no teeth erupt on time or when the first teeth show up in an unusual position and with an aberrant form. In many of the other >190 different ED forms, there are even greater difficulties in getting to a diagnosis.

In recent years, the internet has had an enormous impact on access to information. The successful initiative of Mary Kaye Richter, who thirty years ago started the first support group in the US, has had many followers, and today the International ED network (IEDN) covers four continents. However, individuals and families with ED suffer the same difficulties that are typical for all rare disorders in search for physicians and dentists who can help, treat and give advice for good quality of treatment to assure a good quality of life. Recent research has led to a better understanding of symptoms not only in ectodermally derived tissues, but also in tissues of mesenchymal origin. The last decade has seen a veritable eruption of new knowledge, not only in the genetic field, but also in diagnostics and treatment. The most spectacular scientific contribution was when X-linked hypohidrotic ED as the first heritable disease was shown to be permanently corrected by treatment with the missing protein. Now we are following the application of these findings from mice to men. This also calls for estimations of prevalence, ethical considerations, more research and hope for a better future for individuals with ED.

I2 Early recognition of hypohidrotic ectodermal dysplasia
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Head & Face Medicine 2012, 8(Suppl 1):I2

Hypohidrotic ectodermal dysplasia (HED) is characterized by severe hypohidrosis, hypoplasia of sweat, sebaceous, submucous, meibomian and mammary glands, hypotrichosis, and oligodontia. In early childhood, HED is a life-threatening disorder based on the risks for hyperthermia and pneumonia. Awareness of the hazards related to this rare genetic disease is most helpful in preventing avoidable calamities. Prognosis therefore depends on the time point of diagnosis.

Typical facial features (frontal bossing, sparse eyebrows and eyelashes, wrinkling and hyperpigmentation of the periorbital skin, saddle nose, everted lips, hypoplastic mandible) may allow immediate postnatal recognition of HED, if the disease is known to the family or the doctor. Molecular analysis of one or more of the 4 candidate genes EDA, EDAR, EDARADD and NEMO can then be arranged to make a definitive diagnosis. Infants with HED may also be identified by their inability to sweat. A survey conducted among parents of 100 children with ectodermal dysplasia registered with the German-Swiss-Austrian patient support group revealed that almost all parents had observed episodes of unexplained fever during the first year of life. If infants had to be placed in an incubator after birth, body temperature recording proved to be of utmost importance and often allowed early clinical diagnosis of HED. Furthermore, recent studies of our group confirmed a consistent, quantifiable defect of sweat gland function in male individuals with HED as a disease biomarker. Pilocarpine-induced sweat volume, palmar or plantar sweat duct density and skin conductance before and after stimulation were determined also in newborn infants. Genotype-phenotype correlation was seen across all measurements of sweat gland function, but, surprisingly, not with respect to the number of sweat glands (which can be determined very soon after birth) and the degree of oligodontia (diagnosable already by prenatal ultrasonography). This is important, since such easily recognizable signs obviously do not allow prediction of the risk of hyperthermia and the associated morbidity and mortality in HED patients.

I3 Involvement of the ocular system in hypohidrotic ectodermal dysplasia
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Head & Face Medicine 2012, 8(Suppl 1):I3

X-linked hypohidrotic ectodermal dysplasia (XLHED) is the most common form of ectodermal dysplasia. It often presents with ocular symptoms, already in early childhood. Multiple ophthalmological tests are available, but in early childhood only tests of lower invasiveness can be applied. We have evaluated tear film tests and ocular surface staining as screening methods in pediatric patients with signs of ectodermal dysplasia. These tests may also be used in adults with confirmed XLHED to determine the severity of ocular surface disease.

Twelve children and 14 adults with XLHED were subjected to a panel of tests including the ocular surface disease index (OSDI), non-invasive
measurement of tear film break-up time (NIBUT), osmolarity, Schirmer test, lissamine green staining, fluorescein staining, meibography and infrared thermography. Sensitivity and specificity were determined for single tests and selected test combinations. For adults with XLHED, OSDI, NIBUT and osmolarity were the best single routine tests (sensitivity between 84.6% and 85.7%; specificity of 100%). Their combination increased the sensitivity to 92.8%. Meibography yielded optimal results (100% sensitivity and specificity). Infrared thermography revealed a typical pattern for XLHED. In children with XLHED, NIBUT or OSDI were the most convincing single tests (sensitivity of 90.9% and 83.3%, respectively; specificity of 100% each), combination of which increased the sensitivity to 100%. More invasive tests such as meibography and infrared thermography led to good results if they were tolerated.

Tear film tests can help to establish an early diagnosis in individuals with suspected XLHED, even before genetic test results are available. Meibomian gland disorder and resulting hypervaporative dry eye are typical features of XLHED. Once the diagnosis is made, tear film tests are an important instrument to establish an effective therapy of dry eye disease.

14 Dermatologic aspects of ectodermal dysplasias
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Head & Face Medicine 2012, 8(Suppl 1):14

Ectodermal dysplasias are a large group of heterogeneous heritable conditions characterized by congenital defects of ectodermal structures and their appendages: hair (hypotrichosis, partial or total alopecia), nails (dystrophic, hypertrophic, abnormally keratinized), teeth (enamel defect or absent) and sweat glands (hypoplastic or aplastic). The ectodermal dysplasias, as a rule, are not pure "one-layer diseases". Mesodermal and occasionally endodermal dysplasias may coexist. Embryogenesis occurs in distinct tissue fields and specific interactions among the germ layers that may lead to a wide range of ectodermal dysplasias exist when genes important for development are mutated or otherwise altered in expression. Of the approximately 200 different ectodermal dysplasias, about 50 have been characterized at the molecular level with identification of the causative gene. Modern molecular genetics will increasingly elucidate the basic defects of the different syndromes and yield more insight into the regulatory mechanisms of embryogenesis.

This lecture focuses on the fact that with molecular diagnosis it is possible to diagnose oligosymptomatic forms of ectodermal dysplasia. These are much more common than earlier anticipated. Cutaneous key features which give hints for the presence of some type of ectodermal dysplasia will be presented.

15 Prosthodontic treatment of patients with ectodermal dysplasia
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Head & Face Medicine 2012, 8(Suppl 1):5

The definition of "health" as provided by the World Health Organization (WHO) points out that this status is not only given by the absence of disease and infirmity – but that social well-being is an inherent parameter for a healthy subject. Within medicine and dentistry, individuals with ectodermal dysplasia represent a very special group of patients. Diagnostics and treatment planning have to start early in childhood. Furthermore, this disease requires the early cooperation of three disciplines of our profession: prosthodontics to define the final outcome at a later, adolescent age, and both orthodontics and maxillofacial surgery to accompany and treat the patients in an ongoing/stand-by way. Treatment decisions of the dental team depend on the patients' needs, wishes, their willingness to undergo minor or major treatment with different impact, and also on the economic possibilities. Therapeutic options normally range from lining up existing teeth according to a final treatment plan to preliminary dentures and – at the end – to bone grafting and dental implants, often followed by extensive restorative/prosthetic therapies. Different prosthetic devices may be indicated and the patients need to be encouraged for an appropriate treatment.

16 The young adult patient presenting with oligodontia: diagnostic and management strategies
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Head & Face Medicine 2012, 8(Suppl 1):6

Patients with various forms of ectodermal dysplasia often present with oligodontia, aplastic dento-alveolar ridges, malformed teeth and hypoplasia. Management and support follow a continuum from early childhood to adulthood. In addition, management strategies impact on the patient's perceived quality of life (QOL) as well as on the outcomes of care.

The role of the Prosthodontics team is to diagnose, educate and provide care plans that address the range of issues concerning the young adult needing tooth replacement therapy. These often involve ceramic restorations, oral implants and fixed and removable prostheses. Ultimately, the diagnostic phase is critical and requires an interdisciplinary care team leading to rational care plans. Long-term data with regard to oral implant outcomes, complex reconstructions and the impact on QOL will be discussed. There are ranges of treatment options with different advantages and challenges. The young adult with ectodermal dysplasia therefore needs to understand the critical points of assessment, the process of informed consent, the individual care plan, and the possible outcomes of care when electing to perform tooth replacement.

17 Soft tissue handling and dental implant treatment
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Head & Face Medicine 2012, 8(Suppl 1):7

Ectodermal dysplasias are a heterogeneous group of inherited disorders characterized by defective formation of tissues derived from the embryonic ectoderm. Besides tissues of epidermal origin, other maxillofacial structures including hard and soft tissues can be affected. Disturbances in the early development of teeth frequently result in congenital absence or deformities of teeth. The lack of teeth leads to an impaired development of the alveolar crest, with decreased vertical and horizontal dimension. Osseointegrated dental implants in combination with hard and soft tissue augmentation techniques can be used successfully to restore the patients' masticatory function, phonetics and aesthetics.

18 Pathogenesis of ectodermal dysplasia
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Head & Face Medicine 2012, 8(Suppl 1):8

Ectodermal dysplasias (ED) are characterized by impaired development of organs forming from the embryonic surface ectoderm. Thus, in ED organs like teeth, hair, nails and exocrine glands are hypoplastic or totally missing. The pathogenesis of the defects is starting to be understood thanks to the identification of the responsible gene mutations, and to the advances in developmental biology. Rapid progress particularly in genetics and in the generation of genetically modified animals such as transgenic mice has allowed the exploration of events leading to ectodermal organ defects at the cellular and molecular levels. Mouse models have been produced for many different ED syndromes. Most work so far has focused on hypohidrotic ED which is caused by mutations affecting the ectodysplasin (Eda) signalling pathway. Analyses of mouse mutants in which Eda signalling is either blocked (like in most patients with hypohidrotic ED) or overactivated have indicated that Eda signalling is a key regulator of ectodermal placodes. The placodes initiate the formation of ectodermal organs, their positions determine the location of these organs, and their size is associated with organ size. Eda signalling also affects later stages of development, influencing for instance the shape of teeth and branching of salivary and mammary glands. Recent data indicate that Eda signalling is intimately linked to many other signalling pathways, e.g. Wnt, BMP, and FGF pathways,
which regulate cell communication together with Eda. The detailed understanding of the functions of these molecular networks can be expected to lead to new possibilities to prevent and treat ED.

Animal models of ectodermal dysplasia
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Head & Face Medicine 2012, 8(Suppl 1):9

Various forms of ectodermal dysplasia (ED) have been identified in animals. These animal models of ED may help in our understanding of the pathogenesis of ED and the development of novel therapeutic approaches. Mice, dogs, and cattle with mutations in the X-linked EDA gene have been reported and show clinical features that closely resemble X-linked hypohidrotic ectodermal dysplasia in humans. We still do not completely understand the complex signaling pathways, which are required for the normal development of the various ectodermal appendages. Spontaneous animal mutants offer the chance to identify additional components of this complex regulatory network. One such example is represented by the hairless dogs. Different breeds of hairless dogs such as the Mexican and Peruvian Hairless Dogs or the Chinese Crested Dog have been bred by dog fanciers for many centuries. These dogs have a sparse hair coat and dentition abnormalities similar to EDA mutant dogs. However, in contrast to EDA mutant dogs, the eccrine glands in the above mentioned hairless dogs are normal. We identified a mutation in the gene encoding the transcription factor FOXI3 as causative for the ED phenotype in hairless dogs. The phenotypic similarities between EDA and FOXI3 mutants suggest that FOXI3 is somehow involved in the ectodysplasin signaling pathway. However, the precise role of FOXI3 in ectodermal development has not yet been completely clarified.

Novel genetic findings
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Here we report on the clinical findings and key symptoms in WNT10A-related ectodermal dysplasias. The ectodermal dysplasias (ED) are a large, heterogeneous group of disorders characterized by defects in the morphogenesis of skin, sweat, sebaceous, submucous, and mammary glands, hair, nails and teeth. Numerous more or less distinct entities have been reported, however, most of them are very rare and the cause is often unknown. EDA mutations, resulting in hypohidrotic ectodermal dysplasia (Christ Siemens Touraine syndrome) are known as the most common cause of ED. Over the last two years, WNT10A has turned out to be the second major gene associated with ED. WNT10A mutation carriers present with a broad and variable spectrum of symptoms related to at least four known Mendelian conditions as there are autosomal dominant Selective Tooth Agenesis Type 4 and autosomal recessive Adontia of Permanent Dentition (APD), Odonto-Onycho-Dermal Dysplasia (OODD), and Schöpf-Schulz-Passarge syndrome (SSPS). In heterozygotes, penetrance is reduced and only about half of the carriers show a phenotype including mainly tooth and nail anomalies. Approximately 8% of the unaffected individuals in our control group carried a WNT10A mutation. Further studies are necessary. We conclude that WNT10A mutation analysis might become an important diagnostic test in many patients with selective tooth agenesis or severe oligodontia concerning the permanent teeth.

Heterozygote manifestations in X-chromosomal ectodermal dysplasia
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About 60-70% of the heterozygotes of X-linked hypohidrotic ectodermal dysplasia (XLHED) show some clinical manifestations of the disease. Dental abnormalities are key diagnostic features and can be best evaluated at a young age. Compared to controls, carriers have a significantly higher frequency of agenesis of permanent teeth with persistence of deciduous teeth, small teeth resulting in gaps between the teeth, and peg-shaped teeth. Whole saliva flow seems to be reduced in carriers, whereas concentrations of most inorganic salivary constituents and total protein are higher than in controls. Craniofacial morphology of carriers shows some subtle deviations such as short and retrognatic maxilla, protruding lips, and a shorter total facial height compared to controls, findings that could be explained in part by hypodontia. Mild hypodontia and mild hypohidrosis are two further commonly seen carrier signs. No correlation has been found so far between the type of mutations, the patients’ phenotypes and disease severity. The mosaic-like distribution of normal and abnormal skin along the Blaschko lines is a typical consequence of the clonal inactivation of the X-chromosomes. While carriers with a highly skewed X-chromosome inactivation pattern may show pronounced clinical features due to the unequal expression of the two alleles (‘functional hemizygosity’), no correlation has been found between the severity of clinical symptoms and X-chromosome inactivation in leukocytes of carriers. Sporadic cases of males with XLHED and autosomal recessive HED (arHED) cannot be distinguished clinically. In contrast to heterozygotes of XLHED, who frequently show mild involvement, heterozygous parents of patients with arHED show no features of the disorder. However, because of the highly variable expression of XLHED in carriers, phenotypic assessment may result both in underdetection and false-positive diagnosis.

Hypohidrotic ectodermal dysplasia and physical exercise
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Head & Face Medicine 2012, 8(Suppl 1):12

Because of their lack of sweat glands, individuals with hypohidrotic ectodermal dysplasia (HED) are assumed to be at risk of severe hyperthermia during exercise in a warm environment. If pediatric HED patients ask whether they may practice competitive sports, most physicians are hesitant to give recommendations other than swimming, which is unlikely to lead to life-threatening exertional overheating. To study the effects of physical exercise on HED patients more systematically and to determine levels of activity they tolerate and may engage in without health hazards, 13 boys and male adolescents with X-linked HED as well as age-matched healthy male controls were investigated during standardized exercise on a bicycle ergometer at ambient temperatures of 25°C and 30°C. Protective effects of evaporative skin cooling devices were evaluated at 30°C. Heart rates and lactate values did not differ significantly between HED and control groups. Application of skin cooling devices led to a clinically relevant attenuation of exertional hyperthermia in HED patients, and a previous tendency towards lower performance disappeared. This first systematic study of the effects of physical exercise on HED patients demonstrated a rapid and lasting body temperature increase in HED subjects after cycling, posing them at risk of exercise-induced hyperthermia and heat-related illnesses. External evaporative skin cooling attenuates exertional overheating in HED patients and may facilitate their participation in athletic activities and professional life.

How to keep a patient support group running?
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The achievements and challenges of modern society have an important impact on patients with rare diseases and on the patient support groups...
that have been established in many countries. Although people are now able to exchange information from one corner of the world to another just in a minute via internet, personal relationships and wholehearted personal communication have remained the best ways to share experiences and to support each other. Nowadays patient organizations may also contribute to shaping patient-centred health policies by describing their experiences and expectations on diagnosis and care. Networking with medical experts often leads to improved access to medical services and novel research findings. We will report on the experiences of two young patient associations in Mexico and Poland.

### I14
**Treatment of oral dysfunction**

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Head & Face Medicine 2012, 8(Suppl 1):14

The orofacial area is central for several vital functions such as breathing and eating. The orofacial area also acts as the basis for social interaction, emotional communication, facial expression and speech communication. Normal orofacial sensorimotor development is necessary for these functions to develop and mature in the child, hence orofacial dysfunction may be severely disabling. In the oral cavity, saliva lubricates the hard and soft tissues. Lack of saliva impairs speech clarity, chewing and swallowing, taste and voice quality. The complexity of these functions means that several clinical professionals, such as dentists, gastroenterologists, ENT specialists, phoniatricians or laryngologists, and speech and language pathologists, are needed to address the problems. Through a multiprofessional Nordic cooperation an assessment instrument for orofacial functions was developed, the Nordic Orofacial Test-Screening (NOT-S). In a previous study, 46 individuals with ectodermal dysplasia (ED) were investigated using NOT-S. The most frequently recorded dysfunctions were in the domains chewing and swallowing (82.6%), dryness of the mouth (45.7%) and speech (43.5%). Also hoarseness, a parameter that was added to the test, was found in 32.6% of individuals with ED. The treatment alternatives for these problems include above mentioned specialists and a number of different treatment options, such as surgery to improve anatomical conditions, artificial saliva to lubricate the oral mucosa, sensorimotor training to improve chewing and swallowing, or speech and language therapy to address problems with speech production or voice quality.

### I15
**Long-term results of implant-based functional rehabilitation of patients with ectodermal dysplasia**

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Head & Face Medicine 2012, 8(Suppl 1):15

Functional dental rehabilitation of patients with ectodermal dysplasia (ED) still remains a challenge due to severe hypodontia and underdeveloped alveolar ridges that often preclude implant placement without surgical augmentation. Only few data about technique and timing of augmentation and implant placement can be found in the literature. We have established a surgical algorithm as part of a functional dental rehabilitation concept for ED patients. After clinical and radiographic analysis 8 ED patients with typical hypodontia and underdeveloped alveolar ridges of maxilla and mandible were treated by augmentation with autogenous iliac or mandibular bone. In one case, lateralisation of the inferior alveolar nerve was performed. Three months later implants were inserted and loaded after an interval of 6 months. Sulcus reconstruction with split skin grafts had to be done in three patients. Since then - on average 5 years after loading - no implant has been lost. No sensory deficit has been observed. Based on our results we conclude that in the growing ED patient removable prostheses should be recommended in general, implant placement only in selected cases. When the growth phase is finished, augmentation of the mandible and/or maxilla with autogenous bone may be safely performed, followed by implant placement in a second procedure and loading of the implants. Iliac bone is most often used due to the relatively large amount of bone needed.

### I16
**Ectodermal dysplasia-related disorders of the respiratory tract**

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Head & Face Medicine 2012, 8(Suppl 1):16

Ectodermal dysplasia syndromes are frequently associated with manifestations of disease in the respiratory tract. Commonly, patients present with signs and symptoms of sinusitis, otitis media with effusion, bronchitis or pneumonia. The etiologic bases for these disorders are multifactorial, including abnormal mucous production, anatomical variations, atopy and immune function abnormalities. This presentation reviews the current literature on the clinical manifestations and potential underlying causes for the noted increase in morbidity due to respiratory disease in the ectodermal dysplasia syndromes.

### I17
**The long way from bench to bedside**

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Head & Face Medicine 2012, 8(Suppl 1):17

Loss-of-function mutations in the ectodysplasin A gene, EDA, have been associated with X-linked hypohidrotic ectodermal dysplasia (XL-HED) since 1996. In 2003, we made use of this information to engineer a recombinant soluble form of ectodysplasin A that has the potential to revert the disease in mice. Almost 10 years later, a cure is still not available for individuals affected by the disease. Is this normal? Part of the answer lies in the complexity of the process linking the proof of principle (in mice) and the authority-approved human treatment. It involves the production of a clinical grade pharmacological drug, a tricky process that requires clean-from-the-start-engineering and extensive stability/efficacy/toxicity controls at every step. And this is only the beginning. Defining treatment windows, regimens, doses and biomarkers of efficacy requires significant research efforts; often tedious and unlikely to be published in high-impact journals. Production and research must run in parallel to discussions with regulatory agencies, each process influencing the other. Finally, a wealth of clinical data must be put together, including precise natural history, identification and preparation of clinical centers, clinical trial protocols set up and filing. Taken together, these steps require two things: i) time and ii) dedicated professionals from many different fields: scientists, clinicians, pharmacologists, production experts, regulatory experts and, importantly, a strong industrial partner. It is a fascinating process, subject to delays and pitfalls, but essentially sound as it drives for the development of the safest and best drug possible.
development may vary both between tissues and between species. This was demonstrated in two animal models of XLHED, the mouse and the dog, where a recombinant form of EDA-A1 (EDI200) was administered either antenatally or postnatally. Perhaps surprisingly, in the dog model most analogous to human XLHED, postnatal EDI200 administration was associated with a sustained, reproducible and clinically meaningful correction of the XLHED phenotype.

Detailed studies of the response to EDI200 in both animal models have provided a roadmap for clinical trials involving EDI200 as an EDA-A1 replacement in patients with XLHED. Under consideration for 2012 is the initiation of studies in a small number of XLHED-affected adults and newborns to enable safety testing of EDI200 in these populations and to assess the potential for ameliorating the clinical signs and symptoms. Key aspects of this clinical development plan will be discussed including selection of dose and dosing regimen, the window of efficacy and options for bioactivity monitoring.

**ORAL PRESENTATIONS**

**O1**

Parallel testing of several genes (panel-testing) in patients with ectodysplasin dysplasia using next-generation sequencing
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Ectodermal dysplasia (EDA) is a group of syndromes characterized by abnormalities of structures of ectodermal origin. Up to now more than 150 different syndromes are known. Affected ectodermal structures are mainly hair, teeth, nails and sweat glands. ED can be classified by mode of inheritance (autosomal dominant, autosomal recessive and X-linked), by additional clinical symptoms (e.g. facial abnormalities) or by the structures involved. Hypohidrotic or ‘classical’ ED (EDA) is caused by mutations in the genes EDA, EDAR and EDARADD. Mutations in the X-linked EDA gene underlie most cases. EDAR and EDARADD are known to be associated with both autosomal dominant and autosomal recessive forms of HED. As many ED forms show overlapping clinical phenotypes, often many genes have to be analyzed to identify the causative mutation in a patient, therefore Sanger sequencing frequently takes several months and is laborious and cost-intensive. We have designed an accurate and fast molecular test for the 6 most common ED genes using next-generation sequencing. We developed a novel PCR-based protocol on a Roche 484 Junior platform for mutation screening of the genes EDA, EDAR, EDARADD, TP63, GJB6 and WNT10A. The verification and validation process was finished in October 2011, and the “ED panel” is now the routine diagnostic test for ED in our institute. During the last months several mutations in different genes could be identified with this method. A definitive diagnosis could be made rapidly in a number of so far “unsolved cases”. In summary, the next generation sequencing approach has the potential to increase the diagnostic sensitivity by expanding the number of genes that can be screened in parallel while also reducing expenditure of time and costs.

**O2**

Implants in grafted and native bone in patients with ectodermal dysplasia
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Ectodermal dysplasia (ED) is a congenital syndrome characterized by abnormalities of tissues of ectodermal origin, namely skin, nails, hair, and teeth. Despite the significant progress in treatment of patients with ED is necessary because it provides the opportunity to develop normal speech, chewing, swallowing, and facial support. Because there are few reports on implants inserted in grafted bone in patients with ED, we performed a retrospective study on 44 implants in 4 patients to determine variables that affect survival and crestal bone remodeling around the implant neck in such subjects. Forty-four fixtures were analyzed. Several patient-related (age and sex), anatomic (maxilla, mandible, tooth site), implant (type, length, diameter), surgical (sites and types of grafts), and prosthetic variables (type of loading) were investigated. Implant failure and peri-implant bone resorption were considered as predictors of clinical outcome. Kaplan-Meier algorithm and Cox regression analysis were then performed to detect those variables that are associated with clinical outcome. Implant length and diameter ranged from 11.5 to 15 mm and from 3.5 to 4.0 mm, respectively. Implants were inserted to replace 12 incisors, 12 cuspids, 11 premolars, and 9 molars. No implant was lost. Particular importance of implant length, graft sites, and type of loading was shown by univariate analysis, but these data were not confirmed by multivariate algorithm. In ED patients, dental implants and bone grafts proved to be valuable treatment options which are as effective as in patients not affected by ED, at least in adults. We also analysed the choice to conserve all teeth present in the frontal region. Orthognathic rehabilitation prior to any intervention has been the paramount criterion. In molar regions with tooth agenesis, placement of implants required bypassing of the Nervus mandibularis. In the interfacial region, bone reconstruction was achieved by bone grafting surgery.

**POSTER PRESENTATIONS**

**P1**

Genotype-phenotype correlation in XLHED: insights into the biology of ectodysplasin
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Head & Face Medicine 2012, 8(Suppl 1):P1

X-linked hypohidrotic ectodermal dysplasia (XLHED) is the most common of the ectodermal dysplasias, with a classic presentation of hypodontia, hypohidrosis, hypotrichosis and sebaceous gland hypoplasia. Mutations in the ectodysplasin gene (EDA) underlie XLHED with nearly 200 different mutations reported. EDA encodes a type 2 transmembrane protein of the TNF family (EDA-A1), the active form of which is released from the cell surface following furin proteolytic cleavage. During normal human development, EDA-A1 multimers bind to their cognate receptor (EDAR) driving maturation of ectodermal placodes into sweat ducts, hair follicles, tooth buds, and sebaceous glands. In the absence of functional EDA-A1, all of the above are compromised.

As genotype-phenotype correlations in XLHED have not yet been characterized satisfactorily, natural history studies incorporating non-invasive, quantitative assessments were conducted on 120 genotypeed XLHED males, age newborn to 60 years. This extensive cohort, representing 69 different mutations, can now be analyzed for phenotypic variation associated with alterations in the intracellular, transmembrane, extracellular pre-cleavage, furin recognition, collagen-like domain, and receptor binding regions of the
EDA-A1 protein. Approximately 3/4 of the XLHED patients evaluated had missense or nonsense EDA mutations and 1/4 had indel mutations. In an initial approach to genotype-phenotype correlation, the severe or “null” phenotype (anhidrosis), with absence of both sweat ducts and inducible sweating, was associated with 55 of the EDA genotypes. The remaining 14 EDA mutations were associated with the presence of normal appearing but hypofunctional sweat ducts, highlighting specific regions of the EDA-A1 protein where non-termination mutations allowed for activation of sweat duct development but through aberrant pathways. These experiments of nature may provide novel insights into the biology of ectodysplasin biosynthesis and functional activation of the ectodysplasin/EDAR/NFkB pathway.

**P2**
Phenotypic variability in a cohort of 40 Italian subjects carrying mutations in the gene EDA
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Ectodermal dysplasias (ED) are a group of clinically and genetically heterogeneous conditions commonly characterized by abnormal development of at least two structures derived from the embryonal ectoderm (hair, teeth, nails, and sweat glands). X-linked hypohidrotic ED, which is caused by mutations in the gene EDA (MIM 305100), is the most frequent form. In this study, we investigated the phenotype of 40 male patients, aged 2 to 20 years, who all showed developmental defects of ectodermal derivatives and a mutation in EDA. Special assessments of the involved organ systems were performed. 95% of these patients presented with impairment of sweating, which was only moderate in 35%, while two subjects did not show any alteration of sweat gland function. Severe oligodontia was found in 80% of the subjects, 10% had hypodontia. 90% of the patients showed abnormal crown morphology of the teeth. Severe involvement of the scalp hair was observed in 22% of the patients, moderate involvement in 72%, and no relevant alterations of hair morphology, quantity or growth in 2 patients. Onychodyastrophy was seen in 67% of our patients. Concerning minor alterations of ectodermal tissues, we found dry eye signs in 92% of the subjects investigated, recurrent respiratory infections in 82%, hearing loss in 10%, atopic dermatitis in 35%, and a neuropsychological disorder in 10%. Our study shows that an EDA mutation can be present in males also in the context of only one of the major clinical signs of X-linked ED, but associated with minor alterations. Therefore we suggest that EDA gene analysis should be considered also for males with a mild ED phenotype.

**P3**
Lung and eye involvement in X-linked hypohidrotic ectodermal dysplasia
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Objective: X-linked hypohidrotic ectodermal dysplasia (XLHED; ectodysplasin deficiency) has been classically described as affecting hair, sweat glands and dentition. What may be underappreciated is the effect ectodysplasin deficiency has on glands surrounding the airways and eyes and the resulting chronic health issues. In this study, we evaluated respiratory and ocular symptoms in XLHED patients.

Study design: 12 male children and 14 male adults with XLHED, age range 6 to 58 years, and 12 healthy controls were assessed for signs of asthma by pulmonary function tests and measurement of exhaled nitric oxide (FeNO), and for dry eye disease by investigating ocular surface lubrication.

Descriptive statistics were calculated. Standardized sweat duct counts and EDA genotype were included in correlation analyses.

Results: Respiratory symptoms and elevated FeNO as a sign of pulmonary inflammation were detected in the majority of XLHED subjects, in similar numbers of children and adults. Increased tear osmolality, reduced tear film break-up time and other ocular abnormalities were also present at an early age. Approximately half of the patients not reporting a history of asthma or dry eye showed at least two abnormal test results in the respective organ system. The presence of residual sweat ducts, suggestive of partial EDA gene expression, correlated with milder disease in two XLHED subjects with mutations affecting the collagen-like domain of ectodysplasin.

Conclusions: The high prevalence of asthma-like symptoms and dry eye syndrome in XLHED patients as young as 6 years indicates that screening evaluation, regular monitoring and consideration of therapeutic intervention should begin in early childhood.

**P4**
Genetic counselling of a male patient with hypohidrotic ectodermal dysplasia
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Hypohidrotic ectodermal dysplasias (HED) are characterized by abnormal morphogenesis of epidermis and epidermal appendages. They may be inherited in an autosomal dominant, autosomal recessive or X-linked recessive manner. The most common type shows X-linked inheritance, and males are usually more severely affected than females. In a male infant who was treated in our department, the diagnosis of HED was made 28 years ago. His mother and grandmother also show typical signs of HED in a milder form, while the other family members are all healthy. This young man wanted to know his risk of having affected children. We examined the segregation of X-chromosomes in ten members of the family with 2 intragenic and one extragenic short tandem repeat (STR) markers of the gene EDA (Xq12-13). According to our results, only family members with clinical signs of HED had the same X-chromosome (the affected son, his mother and grandmother), but none of the healthy family members. Direct mutation analysis of EDA was performed, but no aberration could be detected in this gene. Nevertheless, genetic counselling was possible based on the results of the segregation analysis. In this situation, the male progeny of the patient will not be affected, while female progeny will be carriers.

**P5**
Multidisciplinary treatment in children with ectodermal dysplasia
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Oral habilitation in children with ectodermal dysplasia (ED) necessitates consideration of the special dental and oral conditions as well as of the growing child’s physical and psychological development. The severity of ED symptoms varies and is for some families a source of daily worries and complications. The paediatric dentist may be the first professional to suggest the diagnosis of ED since delayed eruption of teeth, aberrant tooth shape and oligodontia are distinct symptoms. Oligodontia may affect chewing ability, speech and aesthetics, so early treatment is often favourable in order to give the child good oral function and appearance. Prevention of dental fear and anxiety is important, since the individual with ED is likely to need dental treatment repeatedly during childhood, adolescence and young adulthood. Therefore, behaviour management methods in combination with an adequate use of sedation and pain control measures are essential. Due to the complexity of treatment planning for children with oligodontia, a multidisciplinary team approach is beneficial and the team should preferably include the disciplines of paediatric dentistry, orthodontics,
prosthetic dentistry, and maxillofacial surgery. The patient and the parents should always be involved in the treatment planning and be informed about short- and long-term treatment options. Aesthetic improvement of existing teeth should be done early if requested. Removable dentures at an early age may also be beneficial for some children. Treatment with fixed dental prostheses should be evaluated at early school age according to individual needs and indications. Examples of multidisciplinary treatment in three children with ED treated in the framework of free dental care for children in Sweden will be presented.

P6
Early dental intervention in patients with X-linked hypohidrotic ectodermal dysplasia
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Introduction: Familiar or syndrome-associated hypo-, oligo or anodontia in children and adolescents demands for professional dental intervention, because poor dental function and aesthetics often result in psychosocial deprivation. Treatment challenges in these patients are to develop functionally and aesthetically acceptable intermediate solutions that strive for tooth and bone preservation and allow for dental growth.

Patients and methods: Fifteen patients with X-linked hypohidrotic ectodermal dysplasia (XL-HED) were treated at the paediatric division of our department, aiming at early intervention and oral improvement. Median age at initial presentation was 4 years. Fourteen patients showed oligodontia with 10.2 missing permanent (5.6 primary) teeth in the upper jaw, and 13 patients lacked 11.5 permanent (8.5 primary) teeth in the lower jaw. One patient had complete anodontia, another one had no teeth in the lower jaw. All oligodontic patients presented with cone-shaped teeth. None of the patients had any first permanent premolar or lateral incisor. In the lower jaw, no central incisors were present. All patients were provided with prostheses to improve masticatory function, vertical height and aesthetics. In addition three patients needed orthodontic intervention to align displaced teeth and improve aesthetical appearance. Cone-shaped teeth were modified with composites in 9 cases, one patient received veneered stainless steel crowns, and in one case ceramic crowns were inserted.

Results and conclusion: Re-adaption of the prosthesis had to be undertaken on an individual basis according to growth. Mean time for prosthesis renewal was two years. All patients were cooperative with respect to the dental intervention. Only one patient did not accept to wear his dentures. Early intervention with conservative and prosthetic measures is a well-accepted and feasible therapeutic concept in the young patient with hypohidrotic ectodermal dysplasia.

P7
Oral rehabilitation with implant-supported overdenture (ISO) in four children with ectodermal dysplasia
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Introduction: Ectodermal Dysplasias (ED) are a heterogeneous group of inherited disorders characterized by dysplasia of tissues of ectodermal origin. Complete or partial anodontia are the most frequent dental findings. Prosthetic rehabilitation is recommended from functional, aesthetic, and psychological points of view. Because of the anatomical abnormalities of existing teeth and alveolar ridges, conventional prosthetic rehabilitation in young patient is often difficult.

Patients and methods: Four growing patients (age 9 to 11 years) with oligo- or anodontia were prosthetically rehabilitated. Panoramic film and Cone Bean Computerized Tomography were performed and a resin model of mandibular bone was made. Despite a remarkable multi-dimensional atrophy of the alveolar bone, the insertion of two tapered implants was possible. After a submerged healing period of 2 months, the implants were exposed and abutment connection was performed. Implants were connected with an expansion bar that permits mandibular growth and prosthetic retention. A removable prosthesis was constructed with ball attachments. Mandibular growth was followed and evaluated using the expansion guide and cephalometric radiographs.

Results: Mandibular growth in sagittal and transverse direction had no adverse effects on implant position. The expansion bar permitted the undisturbed growth of the mandible. After 3 years of follow-up, this study showed that ISO may improve oral function, phonesis and esthetics.

Discussion: The mandibular rotation accompanying growth had not caused a significant problem relative to the angulation of the implants. Implants can be successfully placed, restored and loaded in growing ED patients. The cephalometric analysis supported that ED patients show midface hypoplasia with a class III tendency, which can be avoided by early rehabilitation. Thanks to the good stability and retention of the ISO, patients considered the prostheses as comparable to natural teeth.

P8
Oral manifestation of Goltz-Gorlin syndrome in a young girl
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Introduction: Focal dermal hypoplasia (Goltz-Gorlin syndrome) is a multi-system disorder characterized by involvement of skin, skeletal system, eyes and face. It is caused by loss-of-function mutations in the PORCN gene. We report the case of a young female, focusing on the dental features.

Aim: To describe the oral manifestation of a rare disorder that resembles ectodermal dysplasia (ED).

Case report: Clinical, radiological and genetic findings revealed common features of Goltz-Gorlin syndrome and pure ED. Oro-dental characteristics of the patient mostly corresponded to those described in the literature. However, previously unreported oro-dental findings such as taurodontism, peg-shaped teeth and microdontia are considered unusual for Goltz-Gorlin syndrome, but similar to the dental features of hypohidrotic ED. Clinical characterization of the patient by a multidisciplinary approach is described and a comprehensive review of the literature is presented.

P9
Oral manifestations in a boy with X-linked reticulate pigmentary disorder
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Introduction: X-linked reticulate pigmentary disorder (XLPDR) is a rare, multi-systemic disease with only a limited number of families described in the literature. XLPDR has a genetic origin and the gene has been mapped to Xp22-p21. Dental features resemble those of hypohidrotic ectodermal dysplasia.

Case report: A 3-year-old boy was seen at the Department of Maxillo-Facial Surgery and Paediatric Dentistry of the Children’s Hospital of Trieste. The multi-systemic features of XLPDR included a number of oro-dental manifestations such as misshapen teeth, scissor bite, swallowing difficulties, agenesia of the permanent second premolars, taurodontism, early
resorption of deciduous roots, and premature tooth eruption in general. Other important characteristics are crowding of permanent inferior tooth crowns, severe gingivitis, enamel hypoplasia and discoloration due to multiple antimicrobial treatments.

Discussion: XLPDR is a rare form of ectodermal dysplasia with multi-systemic manifestations requiring intensive medical supervision. Clinically, the oro-dental phenotype resembles that of hypohidrotic ectodermal dysplasia, but there are several novel, previously unreported features.

P10
Prioritization of treatment: need- or desire-based approach with a three-year follow-up
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In general, medical teams do not prioritize treatment in a way to establish mental health prior to other parts of a treatment sequence. Patients with ectodermal dysplasia may not be compromised systemically, but mentally they surely are. In cases of ectodermal dysplasia, the psychological inadequacy may be attributed to the characteristic facial appearance and the absence of teeth. Such cases can be better managed by prioritizing treatment, choosing a desire-based approach rather than a need-based course of action. Improving the facial appearance first will strengthen the confidence of the patient in the operator and increase his overall acceptance in the society. Overcoming psychological barriers allows intra-oral rehabilitation with lesser effort and increases its success.

P11
Follow-up care of rare diseases in odontology: a public health issue
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This study aims at providing new data relating to rare diseases with or without bucco-dental component. A national investigation based on a questionnaire has been carried out in France and a clinical study has been completed with the patients consulting the national centre of rare malformations of the face and the buccal cavity, in particular oligodontia. The results revealed a difficult and complex course of care for all the patients suffering from rare diseases. The oral health quality is not linked to the severity of the bucco-dental component. An unfavorable medico-economic impact has been noted in the treatment of numeric anomalies of teeth, including oligodontia. Proposals have been raised to improve the follow-up care of these patients on the basis of the current evolution of health policy.