Genomics & genetics of the human voice

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Abstract

- ***An overview*** **of genetics and genomics of the human voice is presented.** ***Integration of genetics*** **into the voice area holds a great potential for a better understanding of the complex relationship between static genetic predisposition and dynamic environmental factors and their consequences for health maintenance, disease development and personalized treatment.**
- ***One of the problems is the combined voice, respiration and swallowing interference in the larynx*****. Another problem is that many known genetic deficiencies are related to, or are provoked by e.g. infections in the larynx.**
- ***Phenotypes can be difficult to differentiate*** **based on heterogeneity and polymorphism. Although some progress has been made in complex diseases, such as metabolic syndrome, cardiovascular-cancer diseases and others, genetics of voice related disorders remain quite unknown for most of voice specialists and scientists.**

Overview

Voice diagnostics and therapy related genetics, pharmacogenetics and personalized medicine

Tissue engineering, cellular actions, micro array (light and electronic microscopy aspects)

Organization of personalized medicine in voice disorders

Voice related genetics, pharmacogenetics and personalized medicine

- based on our own studies..

The human genome sequence has been completed and is under investigation. The **integration** with genetics holds a great potential value for a better understanding of the complex relationship between static genetic pre-disposition and **dynamic environmental factors** and its consequences for health maintenance, disease development and personalized treatment.

Genetics of voice related disorders remain quite unknown for most of voice specialists and scientists. Technological advancements have been profuse but must be considered as the foundation of current and future progress on voice.

Modern sequencing platforms, microarrays, high-through put detection technologies, gene transcript profiling, quantitative multiplexed proteomics and nutrients/metabolite analysis should be the key tools achieving the developments in personalized treatment and predicting the rehabilitative process in voice. Establishing and managing good updated databases are further tools to retrieve, visualize, validate, interpret and cross-correlate this data. A great challenge is ahead.

Genetic treatment aspects of upper airways..

- life style, training, education, antihistamines, cortisone and adrenalin (our own research that lead to focusing on genes and personalized medicine)

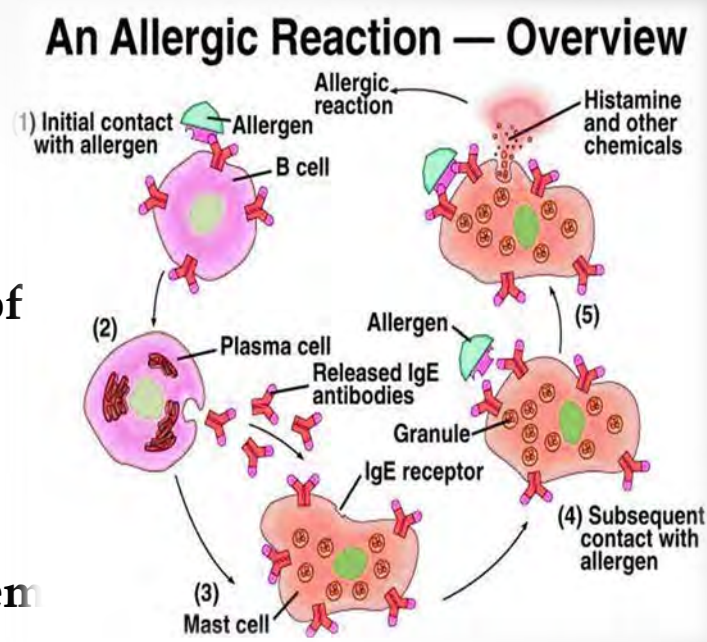
- Pedersen M, Eeg M, (2012) **Does treatment of the laryngeal mucosa reduce dystonic symptoms?**

  Pedersen M., Eeg M. (2012). Does Treatment of the laryngeal mucosa reduce dystonic symptoms? A prospective clinical cohort study of mannose binding lectin and the other immunological parameters with diagnostic use of phonatory function studies. *Eur Arch Otorhinolaryngol.* 269(5). 1477-1482

- Pedersen M, Eeg M (2012) **Laryngopharyngeal Reflux**

  Pedersen M (2012) Laryngopharyngeal Reflux – A Randomized Clinical Controlled Trial. Otolaryngol S1:004. doi:10.4172/2161-119X.S1-004

Treatment aspects



Antihistamines :

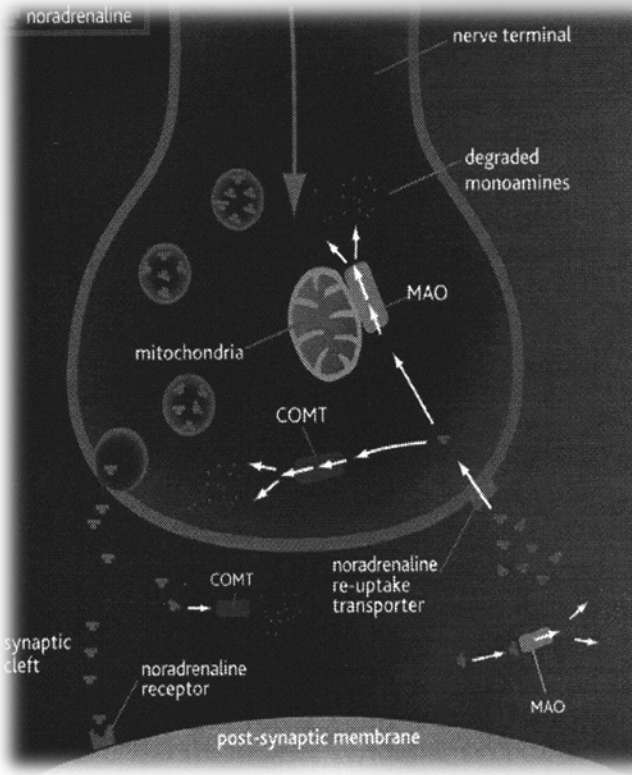
It is generally accepted scientific evident that these **Hl histamine antagonists work by inhibiting the release of histamines on tissues.**

In the event of an exaggerated response to allergens and infections in the body, histamine will be released by granulocytes such as basophiles and macrophages.

These kinds of cells are part of **the innate immune system** picture) **and can be called the first element of immune defense.** On these cells are Fc receptors, which release histamine upon activation. This happens when the IgE antibody attaches to the receptor.

Therefore, **it may require different doses**, as there may be different densities of receptors. When a B-cell is in contact with a allergen such as pollen the cell will proliferate to a plasma cell and begin to release large amounts of IgE antigens into the tissue.

Treatment aspects..



Adrenalin:

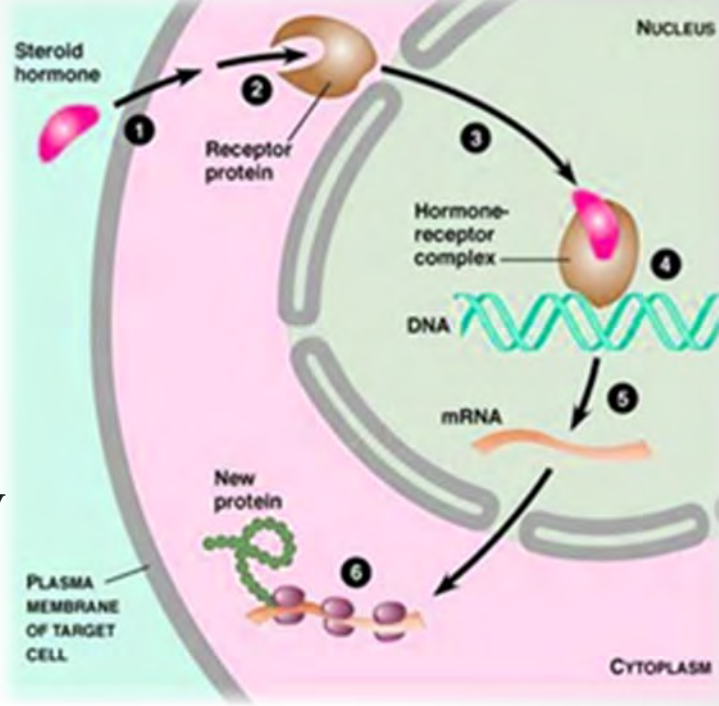
Adrenaline is produced in the adrenal gland and is **a stress hormone that is released during situations that require extra attention to the body**. In such cases where adrenaline is released into the blood
the following happens:
-increased heart rate,
larger displacement of the heartbeat,
raises the-blood sugar concentration, dilation of the pupil.
-contricts the arterioles of the mucous membranes and intestines.
-dilates the arterioles in skeletal muscle by activating the sympaticus system.
By use of a synthetic adrenaline, ephedrine, it can promote the same effects in the body. For example, there will be **a contraction of the arterioles in the nose and throat** (the small blood vessels) or a **dilation of the bronchi** in the lungs. The effect of bronchodilators is used in products like Bricanyl and other more long-acting products. **Therefore this drug can be allergy and infection-relieving.**

Treatment aspects..

Cortisone :

Cortisone is produced by the body, is synthesized from cholesterol in the adrenal gland. All derivatives of cortisone, used for medicinal purposes, are called glucocorticosteroids.

Glucocorticoides effect at the cellular level, functions by binding to cytoplasmic receptor proteins (Receptor chaperonin complex), which then **binds to the cell nucleus DNA.**

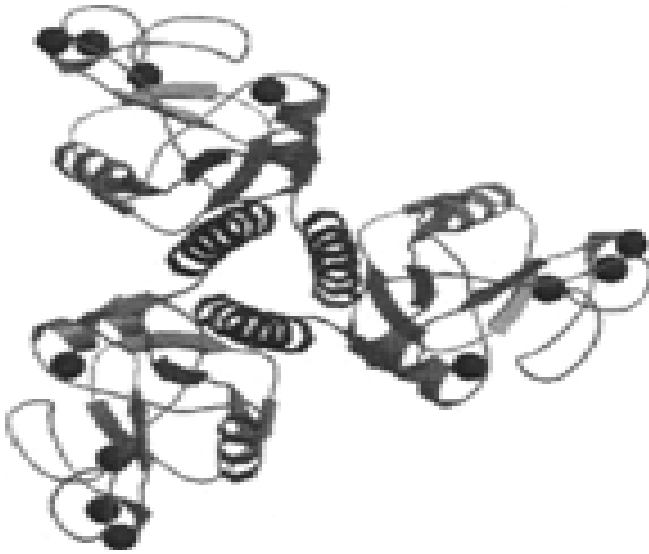


This has an effect on transcription and translation processes, which will affect the cell's impact on the surrounding tissue. Tissue contains different amounts of these receptors which is why glucocorticoids work differently in different tissue.

For example, a regulation of inflammation is seen in mucous membranes and also in upper respiratory tracts.

The binding of DNA happens by a phosphorylation of the hormone receptor complex.

Treatment aspects..



Mannose Binding Lectin diagnostics:

Voice related genetical aspects of mannose binding lectin.

It is a problem not to have enough because it probably indirectly inhibits secondary genetic disorders.

Mannose-binding lectin, **the primitive immunesystem**. This protein is a very important component of the innate immune system (the first defense) because the molecule is designed to recognize carbohydrate patterns on the surface of pathogens (bacteria and viruses, etc.).
Therefore, this molecule has a major influence in the fight against an infection already in the early stages.
Approximately 4% of the Danish population has a mannose-binding lectin <100 μg/L. It is considered low when it is under 500 μg/L.

Tanja the first treated dystonia patient in our cohort study

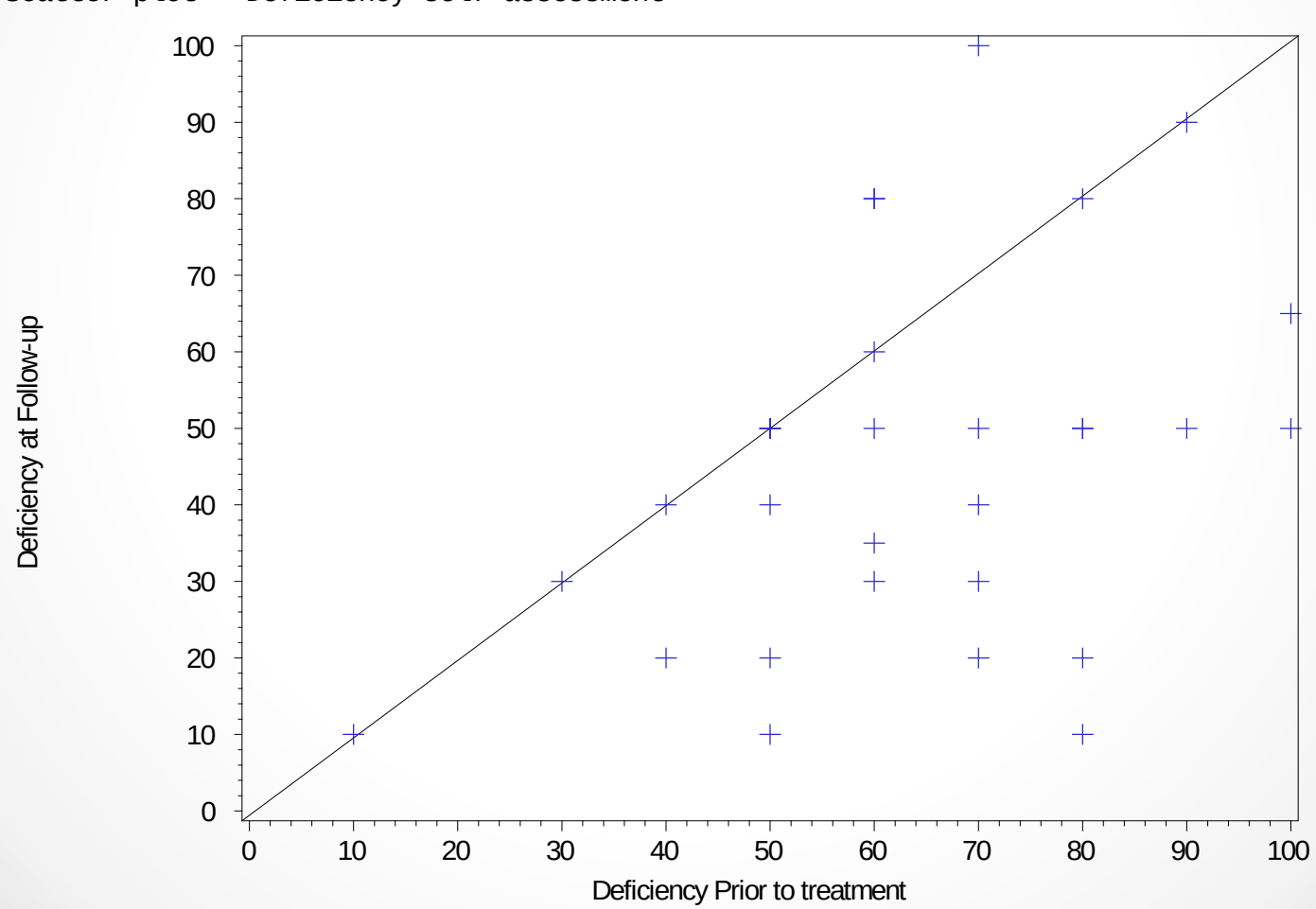
- Tanja was eager to have other dystonia patients examined for eventual mannose binding lectin (MBL)
- We made a prospective cohort study of **55 patients comparing patients with and without MBL reduction**
- We tried to identify other upper airway related disorders in our systematic search for a reason, including genetic lactose and gluten intolerance, food and inhalation allergy – without positive findings

Pedersen M., Eeg M. (2012). Does Treatment of the laryngeal mucosa reduce dystonic symptoms? A prospective clinical cohort study of mannose binding lectin and the other immunological parameters with diagnostic use of phonatory function studies. *Eur Arch Otorhinolaryngol.* 269(5). 1477-1482

Pedersen M., Eeg M. (2012). Does Treatment of the laryngeal mucosa reduce dystonic symptoms? A prospective clinical cohort study of mannose binding lectin and the adrenergic parameters with diagnostic use of phonatory function studies. *Eur Arch Otorhinolaryngol.* 269(5). 1477-1482

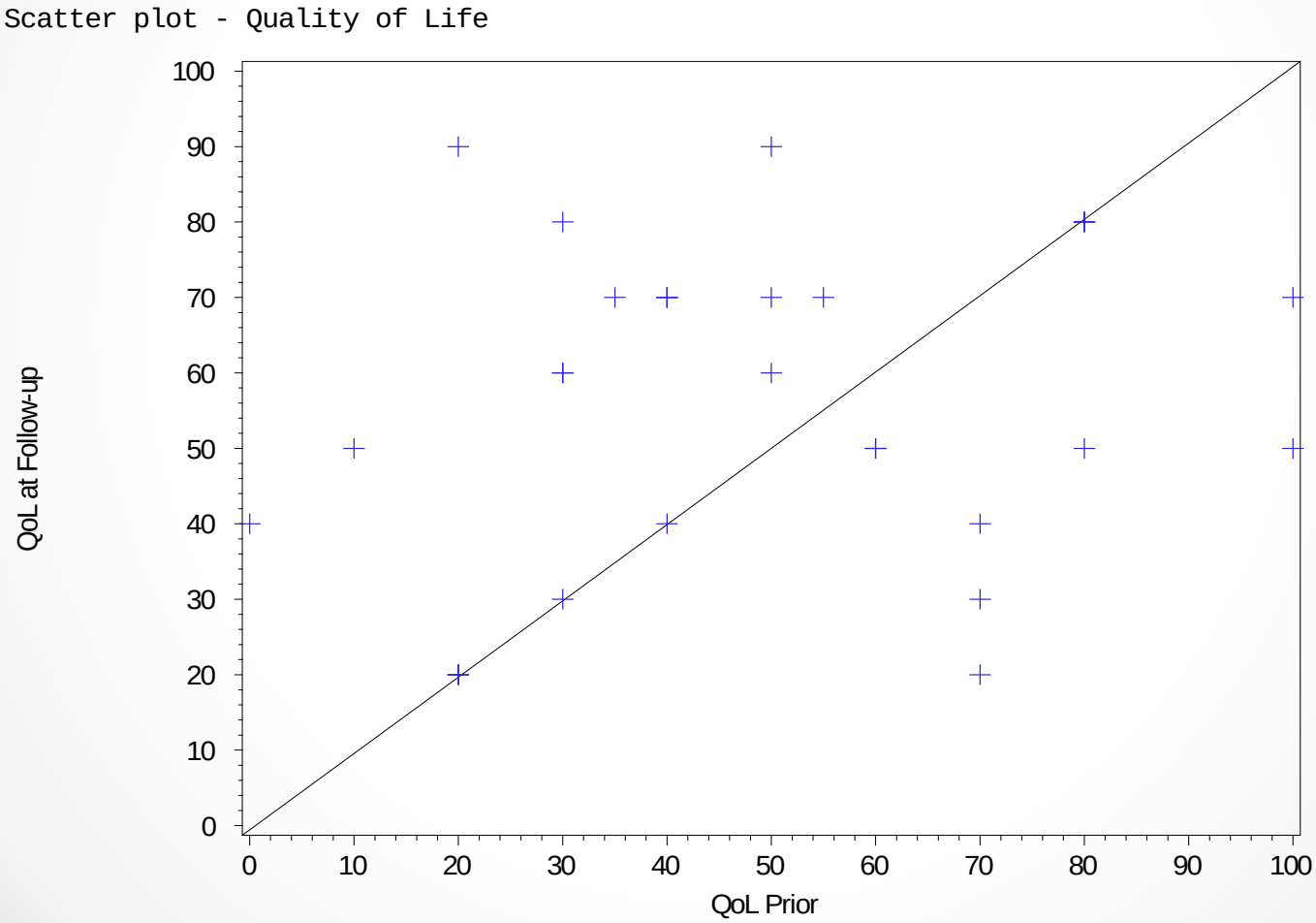
Symptom reduction in 55 patients with dystonia

(absissa deficiency prior to treatment ordinat deficiency at follow-up)



Quality of life in 55 patients with dystonia

(absissa QoL prior ordinat Qol at follow-up)



Laryngopharyngeal Reflux – A Randomized Clinical Controlled Trial

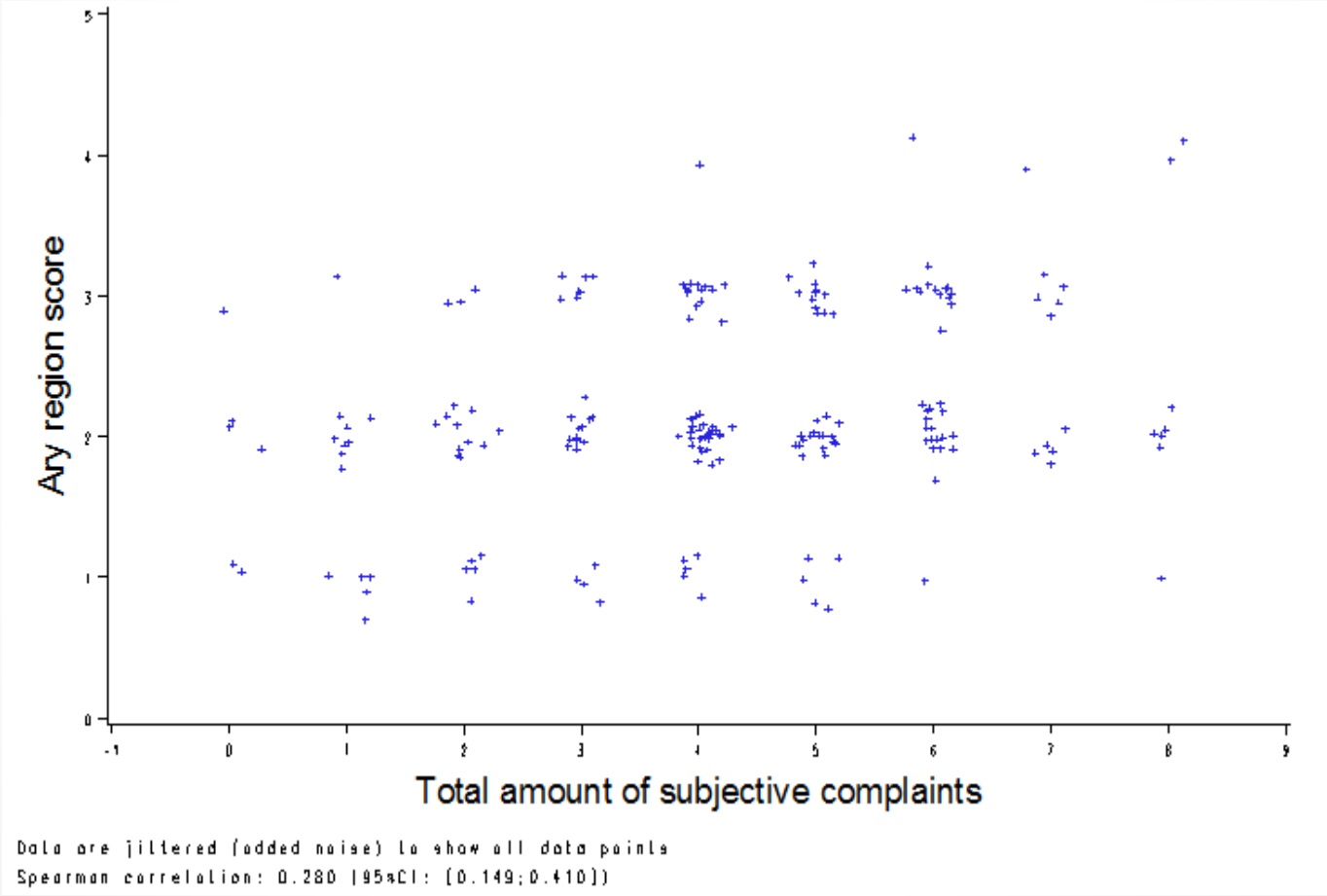
(referring to our Cochrane review 2009).

The following treatments of Laryngopharyngeal Reflux (LPR) were compared: lifestyle advice, lifestyle advice combined with proton pump inhibitor, and life style advice combined with proton pump inhibitor and alginate, based on subjective complaints and documented with high speed films with minimum 2000 frames per second.

A total of 237 patients were randomized based on the planned statistical power calculation of 90%
to detect a difference of 20%, under the assumption that the true difference was 5% and that the standard deviation was 25%

- Pedersen M (2012) Laryngopharyngeal Reflux – A Randomized Clinical Controlled Trial. Otolaryngol S1:004. doi:10.4172/2161-119X.S1-004

Figure 1: Scatter plot of the total amount of subjective complaints (abscissa) versus oedema of the inter-arytenoid region, week 2 (ordinate). Data are filtered (added noise) to show all data points. (Spearman Correlation 0.280 | 95% CI [0.149:0.410]).



Pedersen M (2012) Laryngopharyngeal Reflux – A Randomized Clinical Controlled Trial. Otolaryngol S1:004. doi:10.4172/2161-119X.S1- 004

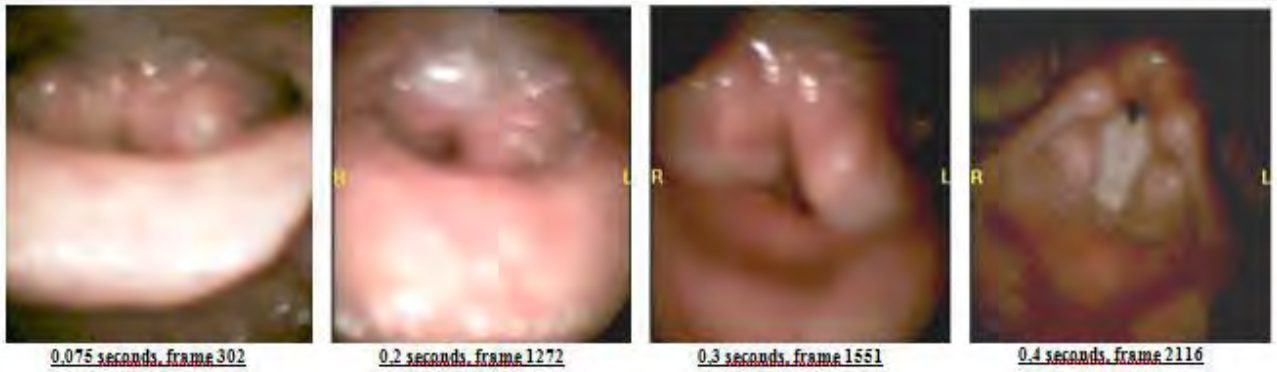
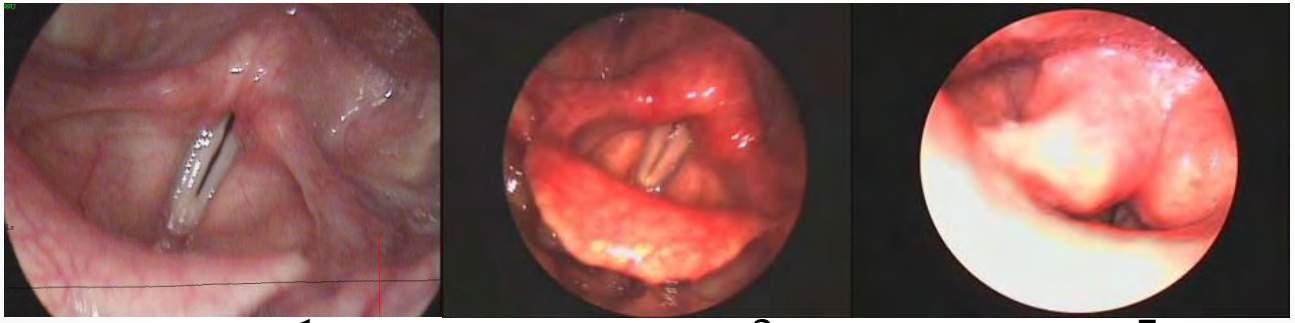


Figure 1: Frames taken from a high-speed video set on recording 4000 pictures per second. The picture, at frame 1272 shows the appearance of mucus in the larynx, and shortly after (frame 1551) it is reduced. On frame 2116, the mucus has disappeared. The process took a total of 0.2 seconds.



score 1 score 3 score 5

Grading of irritation of the arytenoids into grade 1-5
The grading was presented at MAVEBA 2007
Acoustically, a difference was found only between grade 1 and grade 2-5

- Pedersen M (2012) Laryngopharyngeal Reflux – A Randomized Clinical Controlled Trial. Otolaryngol S1:004. doi:10.4172/2161-119X.S1-004

Aspects of literature..
of genetics, pharmacogenetics and personalized medicine

One of the problems is the necessary combined approach of **voice, respiration and swallowing interference in the larynx.**

Another problem is that many known genetic deficiencies are related to e.g**. infections in the larynx.**

A difficulty is the **central nerve system and its relation to periphery genetic voice disorders**, around 300 different syndromes being isolated. Phenotypes can be difficult to differentiate based on heterogeneity and polymorphism.

Education..

How do we change lifestyles - train and educate in our own field?

- **Pharmacogenectics is suffering from lack of integration into clinical practice – also in the voice related area**
- Lack of technical knowledge and awareness could cause severe obstructions on the road to implementing personalized medicine into medical practice.
- **Personalized medicine is a medical model emphasizing in general the customization of health care, with all decisions and practices being tailored to individual patients**

Frueh F.W., Gurwitz D. (2004). From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community. *Pharmacogenetics . 5(5). 571-579*

Genetics and mucosal function..

To follow research of the mucosal immune system is necessary in our field

- **Defects in genes cause immunodeficiency diseases**
  which manifest themselves by enhanced susceptibility to infection or autoimmunity.
- Numerous inherited immunodeficiency diseases have been correlated with susceptibility to particular classes of pathogens.

- The cause of these diseases is the defect protein or glycoprotein encoded by the given mutation in the gene
- Altered gene expression pattern in macrophages is seen in response to interferon-*y* binding to its receptor
- **Recessive and dominant mutations in the interferon-*y* receptor cause diseases of differing severity**

Parham P. (2009). *The immune system*. New York: Garland Science

Applications of genetics..

Applications of genetics and tissue engineering in the practical voice therapy

- **Due to advances in genomics and tissue engineering, new tools and methods are available in voice research**
- Microarray analysis and optical coherence tomography have greatly hastened the development of biochips
- Gene expression profiles, a fundamental part of biochip development, are now commonly performed in some voice laboratories
- Tissue engineering initiatives have led to the ability to grow and work with laryngeal fibroblasts
- **Due to the extreme conditions that vocal fold fibroblasts tolerate, engineering living lamina propria of vocal folds is challenging**

Gray S., Thibeault S., Tresco P. (2003). Witnessing a revolution in voice research: genomics, tissue engineering, biochips and what's next!. *Logoped Phoniatr Vocol.* 28. 7-13

Genetics, personalized vocal exercise..

Development of a personalized vocal exercise (or) rest program, documented with measuring of inflammation and healing

- The development of personalized medicine is a primary objective of the medical community and increasingly also of funding and registration agencies
- Modeling is generally perceived as a key enabling tool to target this goal.
- Agent-Based Models (ABMs) have previously been used to simulate inflammation at various scales up to the whole-organism level
- **Subject-specific simulations also predicted different outcomes from behavioral treatment regimens to which subjects had been exposed**

Li N.Y.K., Verdolini K., Clermont G., Mi Q., Rubinstein E.N. (2008). A Patient-Specific *in silico* Model of Inflammation and Healing Tested in Acute Vocal Fold Injury. *PLoS ONE*. 3(7)

Self-regulation of biological cells..

Biology and self regulation of inflammation and healing of vocal folds – functional genetics and clinical trial aspects. The role of biological cells self regulation have to be analyzed

- Simulations have been used to gain basic insights into the inflammatory response under baseline, gene-knockout, and drug-treated experimental animals
- These simulations have converged with other systems´ biology approaches to aid in the design of new drugs or devices geared towards modulating inflammation
- **These simulations transcend typical cytokine networks by associating inflammatory processes with tissue/organ impacts via tissue damage/dysfunction**
- This frame work has now allowed us to suggest how to modulate acute inflammation in a rational, individually optimized fashion
- **Translational Systems Biology aims to unify mechanisms described in the scientific literature using methods and tools developed by the computational and systems biology communities.**

Vodovotz Y., Constantine G., Faeder J., Mi Q., Rubin J., Bartels J., Sarkar J., Squires R.H. Jr., Okonkwo D., Gerlach J., Zamora R., Luckhart S., Ermentrout B., An G. (2010). *Immunopharmacology and immunotoxicology.* 32(2). 181-195

Bioreactor induced vibrational stimulation..

A mean of harvesting the secreted matrix as a bulk biomaterial by removing the polymer foam using an organic solvent.

- Using the system human derived laryngeal fibroblasts were subjected to vibrational stimuli for 1-21days. Cytokine production, matrix protein accumulation, and construct materiel properties were assessed with DNA microarray, enzyme linked immunosorbent, indirect immunofluorescent, and uni-axial tensile assays respectively.
- The results show that **vocal fold-like vibrational stimuli is sufficient to influence the expression of several key matrix and matrix-related genes**, enhance the secretion of the profibrotic cytokine TGFβ1, increase the accumulation of the extracellular matrix proteins, fibronectin and collagen type 1, as well as enhance construct stiffness compared to non-stimulated controls.

- **The results demonstrate that high frequency substrate vibration, like cyclic strain, can accelerate matrix deposition from human derived laryngeal fibroblasts.**
- The study supports the notion that preconditioning regimens using human cells may be useful for producing cell derived biomaterials for therapeutic application.

Wolchok J.C., Brokopp C., Underwood C.J., Tresco P.A. (2009). The effect of bioreactor induced vibrational stimulation on extracellular matrix production from human derived fibroblasts. *Biomaterials.* 30. 327-335

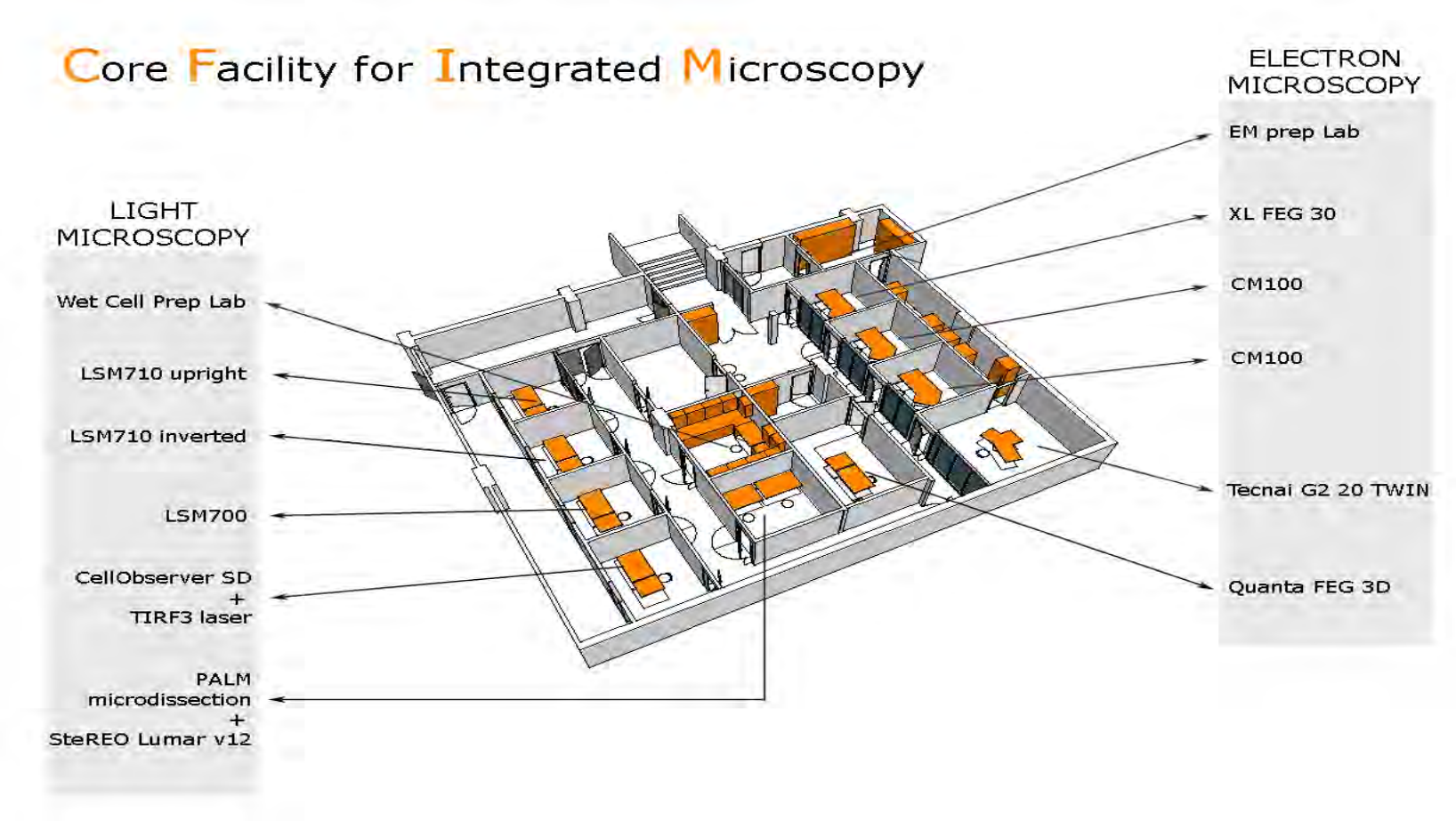
Genetic speech and language deficits are varied..

They are including aphasia, stuttering, articulation disorders, verbal dyspraxia and language impairment.

- Many of the disorders cluster in families, suggesting involvement of genetic factors.
- Mutations in genes *GNPTAB*, *GNPTG* and *NAGPA*, all of which are associated with the lysosomalenzyme targeting pathway, has been reported to cause stuttering
- Comparative studies have shown that genetic variations of ***FOXP2*** **transcription factor is important to the development of speech**. A number of candidate genes regulated by this transcription factor has also been identified
- *CMIP* and *ATP2C2* are associated with language disorders.
- Genetic studies of dyslexia proposed *ROBO1*, *DCDC2*, and *KIAA0319* as candidate genes

Kang C., Drayna D. (2011). Genetics of Speech and Language Disorders. Annu. Rev. Genomics Hum. Genet. 12. 145-64

The facilities at Panum Institut Copenhagen, for light and electron microscopy



Fibroblast synthesis and function related to vibratory micro structure of the vocal cord..

- The special composition and organization in extracellular matrix (ECM) in vocal folds is a critical component in sustaining high frequency vibration.
- Objective: To investigate the effect of vibratory stimulation on ECM gene expression and synthesis of fibroblast in hyaluronic acid hydrogels with approximate viscoelastic properties of vocal mucosa.
- **Results: Indications were found that vibration is a crucial positive factor in restoring ECM structure. It may provide basis for reducing vocal scarring and improvement of voice quality.**

Kutty J, Webb K. Vibration Stimulates Vocal Mucosa-like Matrix Expression by Hydrogel-encapsulated Fibroblasts. J Tissue Eng Regen Med. 2010; 4(1): 62-72.

The human genetic connective tissue studies involve many treatment aspects..

- **The human elastin gene (ELN) is responsible for the generation of elastic fibers in the extracellular matrix of connective tissue throughout the body**
- Individuals with Supravalvular aortic stenosis (SVAS) and Williams syndrome (WS) lack one normal ELN allele
- The perceptual and acoustic characteristics of voice quality for individuals with SVAS/WS, indicates that their voice was significantly more abnormal
- These findings supports the possibility that heterozygous ELN abnormalities negatively influence vocal fold biomechanics

Watts C, Awan S, Marler J. An investigation of voice quality in individuals with inherited elastin gene abnormalities. Clinical Linguistics & Phonetics. 2008; 22(3): 199-213.

Understanding of the elastin genetic function of the vocal folds is necessary with potential

- differential therapeutic aspects..

- Used for this study was five **mice,** *four* with heterozygous elastin (Eln) gene Eln delection (Eln+/-) serving as an animal model for the human disease supravalvular aortic stenosis and *one* normal wild-type control (Eln +/+)-
- Vocal folds were obtained from each animal and stained for the protein elastin using histochemical methods.
- Qualitative visual inspections revealed greater staining density for elastic fibers in the Eln+/+ animals
- Quantitative measurements using digital pixel analysis of staining density revealed significant differences between mice with two genotypes, confirming the qualitative findings
- **Results suggest that Eln requires two functioning alleles for normal structural development of the vocal fold lamina propia.**

Watts C, Knutsen R, Ciliberto C, Mecham R. Evidence for Heterozygous Abnormalities of the Elastin Gene (ELN) Affecting the Quantity of Vocal Fold Elastic Fibers: A Pilot Study. Journal of Voice. 2011; vol. 25, 2: 85-90.[[

Holistic approach e.g. human lymphocytes and leucocytes analysis, how the basic advice for personalized treatment should be made in our field..

- Among the major bottlenecks in translation systems biology into systems medicine are the limited number of clinical cases that can be included in randomized trials and the number of genetic, environmental and nutritional variables that cannot be easily accounted for.

- **Development is necessary of virtual patient models** that mimic the patients' main characteristics, from which testable hypotheses can be generated and validated on the small number of actual patients available.

Auffray C, Charron D, Hood L. Predictive, preventive, personalized and participatory medicine: back to the future.
Genome Medicine. 2010; 2: 57.

Estrogens and Androgens..

Further understanding has been developed in a stratified analysis of voice development in a choir during puberty (8-18 years),

comparing the adrenal and sexual hormonal development with

pediatric and voice parametres,

fundamental frequency and phonetograms

Pedersen M. Development of voice in childhood. Ed. Springer Verlag

Fibroblast growth, biochip development for vocal care..

- DNA does not directly make proteins, it is first transcribed into RNA.
- RNA contains a similar message as the DNA and it is more usable by the cell to make a protein.
- Microarray analysis was used to find the genes. The gene environment interaction cellular and tissue protein, the field of proteomics was found relevant to the area of voice disorders.

- **The use of collagen injection in the vocal cords is a form of protein therapy (as the use of botox)**

Gray S, Thibeault S. Diversity in voice characteristics-interaction between genes and environment, use of microarray analysis. Journal of Communication Disorders. 2002; 35: 347-354.

Restoration of normal gene function might be a possibility..

- The study finds genetic **abnormalities of the ESR1 gene and the HIC1 gene are predictors of late-stage laryngeal cancer and shorter survival**, respectively, for patients with the disease

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- Loss of gene function as a result of abnormal methylation of promoter regions of tumor suppressor genes can be reversed by drugs that can restore normal gene function, opening the door to other treatment options for patients with laryngeal cancer

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- A patient in stage 1, and where we find methylation of ESR1, the patient may have underpinnings of a more aggressive tumor with characteristics that are more in line with a stage 3 or stage 4, refining treatment options

Hopson K. Genes Signal Late-Stage Laryngeal Cancer, Poor Outsome. Henry Ford News. 14-12-2010: 1-2.

Myopathy of voice..

Weakness of voice, how to make future research. It is so important that we follow this genetic research in highly developed centres

- **Distal myopathies represent a heterogeneous group of inherited skeletal muscle disorders**
- One type of adult-onset, progressive autosomal-dominant distal myopathy, frequently associated with dysphagia and dysphonia, has been mapped to chromosome 5q31 in a North American pedigree
- We report the identification of a second large VCPDM family of Bulgarian descent and fine mapping of the critical interval.

- Sequencing of positional candidates genes revealed precisely the same non convertative S85C missense mutation affecting an interspecies conserved residue in the MATR3 gene in both families.
- **Different disease related haplotype signatures in the two families provided evidence that two independent mutational event at the same position in MATR3 cause VCPDM.**

Senderek J, Garvey S, Krieger M, Guergueltcheva V, Urtizberea A, Roos A, Elbracht M, Stendel C, Tournev I, Mihailova V, Feit H, Tramonte J, Hedera P, Crooks K, Bergmann C, Rudnik-Schöneborn S, Zerres K, Lochmüller H, Seboun E, Weis J, Bechmann J, Hauser M, Jackson C. Autosomal-Dominant Distal Myopathy Associated with a Recurrent Mutation in the Gene Encoding the Nuclear Matrix Protein, Matrin 3. The American Journal of Human Genetics. 2009; 84: 511-518.

Virus infection associated with a genetic syndrome is more dangerous..

Tests must be carried out in our field, e.g. respiratory syncytial virus, adenovirus and human papilloma virus

- Infections with adenoviruses are a common problem in the pediatric population.
- Normally asymptomatic to mild, those infections tend to take a more severe course in immuno compromised patients.
- **22q11 deletion syndrom (22q11DS) represents a common genetic disorder causing velopharyngeal dysfunction.**
- Necrotizing enterocolitis (NEC) is a frequent gastrointestinal emergency observed in neonatal intensive care units.
- The occurrence of NEC is more prevalent in preterm infants.

Cichocki M, Singer G, Beyerlein S, Zeder S, Schober P, Höllwarth M. A case of necrotizing enterocolitis associated with adenovirus infection in a term infant with 22q11 deletion syndrome. Journal of Pediatric Surgery. 2008; 43: E5-E8.

Dysphonia is a part of many genetic syndromes and should also be diagnosed with voice analysis e.g. high speed films to understand voice function better in patients..

- 70-years-old Japanese man with **amyloid polyneuropathy** associated with a Val 107 transthyretin (TTR) mutation is reported
- The patient presented with carpal tunnel syndrome, cardiomyopathy, bulbar palsy, dysphonia and polyneuropathy. DNA analysis of the TTR gene revealed a point mutation responsible for substitution of valine for isoleucine at position 107 of the TTR molecule
- **Taken together with reports of patients with the same TTR variant, Val 107 TTR mutation is probably associated with a clinical phenotype characterized by carpal tunnel syndrome, cardiomyopathy, bulbar palsy and dysphonia**
- This case implies a worldwide distribution of the Val 107 TTR mutation with a common clinical phenotype, despite different ethnic background

Nanri T, Utsumi H, Yamada M, Takata Y, Matsumura A, Kougo K, Sekine S, Ogawa D, Toyoda M. Transthyretin Val 107 in a Japanese patient with familial amyloid polyneuropathy. Journal of the Neurological Sciences. 2002; 198: 93-96

Aspects of genetic polymorphism are also necessary in our area. Especially singers need advice of which gene provocation are most important..

Occupational exposures are thought to be responsible for 10-15% of new-onset asthma cases in adults, with disparities across sectors

The study population was composed of subjects who graduated between 2001 and 2006 in bakers and hairdressers sectors where they experience exposure to organic or inorganic allergenic or irritant compounds compared with 250 young workers with no specific occupational exposure.

Subjects were invited to participate in a medical visit to complete clinical and lung function investigations, including fractional exhaled nitric oxide (FENO) and carbon monoxide (CO) measurements, and to collects blood samples for IgE (immunoglobulin E) measurements **Markers of oxidative stress and genetic polymorphisms exploration were also assessed.** A random sample of 200 “non-cases” (controls) followed a nested case-control design

Rémen, Thomas; Coevoet, Vincent; Acouetey, Dovi-St/ephanie; Guéant, Jean-Louis; Guéant-Rodriguez, Rosa-maria; et al. Early incidence of occupational asthma among young bakers, pastry-makers and hairdressers: design of a retrospective cohort study. BMC public health 10 (Apr 26, 2010): 206

299 different syndromes voice related, rarely isolated, probably a under researched area..

- **The paper reports the results of a meta analysis with the aim of documenting the occurrence of voice – and resonance disorders in some genetic syndromes**. The analysis studied the occurrence in general and in different etiological subtypes of syndromes and the association with other disorders, in particular clefting, cognitive impairment and hearing problems
- The database for the analysis was a list of 299 different syndromes all of which had been reported to entail communication disorders
- **Disorders of voice and resonance in genetic syndromes are only rarely isolated problems, an under researched area.** Causal mechanisms are not a major factor in determining the presence of the syndromes

Van J. Voice and Resonance Disorders in Genetic Syndromes: A Meta-Analysis. Folia Phoniatrica et Logopaedica. 2004; 56 (issue 2): 83-92.

Potential gene therapy..

Why are genetics and voice not highly related?

- **The objective of this work is to provide updated guidelines for the evaluation and treatment of girls and women with Turner syndrome (TS)**

- Breakout groups focused on genetic, cardiological, auxological, psychological, gynecological, and general medical concerns and drafted recommendations for presentation to the whole TS group

- It is suggested that parents receiving a prenatal diagnosis of TS be advised of the broad phenotypic spectrum and the quality of life observed in TS in recent years

- It is recommended that magnetic resonance angiography be used in addition to echocardiography to evaluate the cardiovascular system and suggest that TS patients with defined cardiovascular defects be cautioned in regard to pregnancy and certain types of exercise
- **It is suggested that caregivers address the prospect of premature ovarian failure in an open and sensitive manner and emphasize the critical importance of estrogen treatment for feminization and for bone health during the adult years which is also important for the voices**.

[54] Bondy, Carolyn A.; Bondy, C.A. Clinical practice guideline: Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group. Journal of Clinical Endocrinology and Metabolism 92. 1: 10-25. Endocrine Society. (Jan 2007)

Epidermal growth factor receptor is a very promising therapeutic target..

- Cancers of the head and neck and of the lung are associated with high morbidity and mortality rates that have remained relatively unchanged for more than 3 decades
- It is generally believed that the efficacy of standard therapy regimens has reached a plateau for these cancers.
- The discovery of specific aberrant molecular signaling pathways in solid tumors has afforded promising new directions for newer "targeted" cancer therapeutics:
- **The epidermal growth factor receptor (EGFR) shows promise as a therapeutic target.**
- Clinical studies have demonstrated that this targeted approach provides clinically meaningful benefit.

Sattler M, Abidoye O, Salgia R. EGFR-Targeted Therapeutics: Focus on SCCHN and NSCLC. TheScientificWorldJOURNAL. 2008; 8: 909-919

There are genetic relations between benign and malignant genetic disorders..

- Mortality associated with head and neck cancer has remained unchanged for the past decades
- Gene therapy is a novel treatment approach that potentially advance the treatment of genetic diseases.

- Multiple vector systems have been developed that facilitate the introduction of therapeutic genetic material into cells
- **Gene therapy strategies can be classified in 3 groups:**
  - **cytoreductive therapy** aimed at directly inducing cell death
  - **corrective therapy** intended to repair genetic defects underlying malignancy
  - **immune modulation** to promote a robust immune response against cancer

Abuzeid W.M., Li D., O'Malley Jr. B.W. (2011). Gene Therapy for Head and Neck Cancer

Personalizing healthcare: from genetics through payment to improving care..

Interindividual variability in patients' responses to medicines, including the likelihood of toxicity, is commonly due to differences in their genetics

Ultimately, full personalization of medicines will require a better understanding of the systems of genetic pathways rather than just single gene association

- Overall, greater integration of personalized medicine into routine care will require new clinical trial structures. Patient education will also be needed.
- Increasing pressure on resources will also mean that the value of new drugs will come under greater scrutiny, especially if they are adding to choices rather than targeting real unmet need.
- Personalization will reduce the likelihood of failure in drug development. If personalization means less failure, then market fragmentation becomes less hazardous.

Finlayson A, Godman B, Paterson K, Aston E, Haycox A, Gustasson L, Ali R. Personalizing healthcare: from genetics through payment to improving care? J R Soc Med 2013, 106 : 41-44

Conclusion

- The genomic aspects related to the voice and it´s treatment may be dependent on vocal related techniques with light and electronic microscopy as well as optical coherence tomography.

- More basic cellular understanding are upcoming, but pharmacological focus on what really happens with different patients and different treatments over time should be focused upon.

- Some genetic areas have been refered in our introduction today – for voice related pharmacogenetics and personalized medicine.

Thank you for your attention

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