Genetic analysis for early diagnosis of otorhinolaryngeal diseases

Abstract

Familiarity with the concepts and methods of human genetics is important in order to be able to perform genetic analysis. The grade of predictability of a genetic disease is partly given by formal genetics but also depends on the importance of the mutated gene for the phenotype. Possibilities for genetic analysis range from differential diagnosis to predictive diagnosis to prenatal diagnosis. After initial consultation in which the physician fully explains the procedure to the patient, it is mandatory that the patient give his full consent. This article summarises and evaluates current knowledge about genetic analysis of important otorhinolaryngeal diseases, including hereditary hearing disabilities, olfactory malfunction, hereditary tumorous diseases, hereditary syndromes and dysplasias. In addition, this article discusses genetic diseases that affect voice and speech, highlights the relevance of human genetic consultation and discusses the importance of embedding genetic analysis in medicine in general.

Keywords: human genetics, genetic diagnostic procedures, inheritance of otorhinolaryngeal diseases

1 Introduction

Diagnostic procedures in medical laboratories help recognize certain diseases through parameters, which show measurable change due to pathophysiological mechanisms such as elevation of enzymes after tissue necrosis, production of antibodies due to antigen contact or a change in hormonal levels within a feed-back control system. Opposing these pathophysiological phenomena, genetic diagnosis surveys disease aetiology. DNA sequencing is initiated when there is suspicion of a disease caused by genetic alteration. There are numerous genetic mutations within the human genome, as approximately every thousandth base pair is variable, a prevalently genetic polymorphism without functional meaning. Generally, mutations can range anywhere from causing severe malfunction to being functionally irrelevant. The effect a genetic mutation has on the phenotype depends on the influence of the mutation on the gene product, which alters its quality. Thus the relevance of diagnosing a genetic mutation depends on its contribution to the disease. One can easily see this looking at Mendelian inheritance. It is important to understand that human genetics in general are based on formal genetics as well as functional synopses. These principles form the foundation of research and genetic diagnosis and will be explained here in order to fully understand the possibilities and limitations of genetic research.

2 Basic principles of inheritance

2.1 Monogenetically inherited diseases

In human genetics there is a traditional differentiation between autosomally dominant and recessive inheritance. When carrying out genetic analysis, it is important to realise that there are many formal and functional characteristics concerning diseases with simple inheritance.

Autosomally dominant inheritance

In this inheritance a phenotypical alteration is evident, although only one allele is mutated (Figure 1). Here a vertical transmission can be seen, which means that there will be a phaenotypical descent between generations with a 50% chance for each child to inherit the mutation. If the disease-determining mutation is new in the examined patient, the family history will be inconspicuous. This especially applies to severe diseases which often result in non parous patients. Diseases with numerous new mutations occur with a similar frequency in different ethnic groups. The dominant effect is a result of functional disorder, which cannot be compensated through other organism mechanisms. The penetrance of an autosomal dominant mutation can be decreased, penetrance resembling the percentage of mutation carriers displaying the phenotype. If the presence of a mutation is unclear due
Figure 1: The three most common hereditary transmissions. Autosomal dominant transmission indicates that the patient displaying the characteristic feature is heterozygote for the responsible mutation. Full penetrance of the mutation leads to a reliable diagnosis of the genotype through analysing the phaenotype.

In an autosomal recessive inheritance transmission, the patient showing the characteristic feature must have two causative mutations, either homozygote or compound heterozygote. The parents of the patient are phaenotypically inconspicuous, although they are heterozygote. If the mutation responsible for the disease is located on the x-chromosome, this results in a predominance for male patients. Mothers of the patient are phaenotypically inconspicuous (see text for variance). They are heterozygote and thus carriers for the disease.

to this fact, molecular genetic examination can provide answers.

Autosomal recessive inheritance

In an autosomal recessive inheritance both homolog genes are mutated in a homozygote (same mutation) or compound-heterozygote (different mutations) way, resulting in a loss of function (Figure 1). The patient receives one allele from his father and one from his mother. Both parents, and typically their ancestors, are healthy, as they are heterozygote. Siblings are affected on an average of 25% (horizontal transmission). If parents are related to each other, autosomal recessive inherited diseases occur more frequently, as the causal mutation is passed down over a shared relative encounter in the patient. Autosomal recessive diseases occur in different ethnic groups with varied frequency, as the causative alleles are unevenly spread out among ethnic groups due to evolutionary reasons. An autosomal recessive disease occurring in two different ethnic groups can be the result of different mutations within the same allele.

X-chromosomal recessive inheritance

The mutation responsible for the disease is located on the x-chromosome, resulting in a predominance for male patients (karyotype 46,XY) suffering from the disease. Most x-chromosomal inherited diseases are recessive, so females (Karyotype 46,XX) are usually healthy as they carry one unmutated gene with normal function. In this case the normal gene can compensate for the mutated gene. Women are carriers for the disease. The mutation is typically passed down from the mother to 50% of her sons. Brothers of the carrier-mother can suffer from the disease if their mother was also a carrier. Female carriers are commonly unaffected phenotypically, or at least less than male carriers of the mutation. The reason is that one x-chromosome is functionally inactive in all females, as it is almost completely methylated in every cell at an early embryological stage. This prevents transcription of the mutated gene. The process of inactivation is stochastic. Female mutation carriers average 50% of the gene product in comparison with healthy women. In some cases the inactivation process can result in uneven distribution, so that slight symptoms of disease can also occur in female mutation carriers. X-chromosomal inherited diseases can also occur for the first time in a family. In this case, the disease is most likely due to a new mutation. The percentage of new mutations among all patients suffering from a certain disease depends on the severity of the disease. If the disease is so severe that it causes the patients to remain childless (genetic lethality), one third of the patients are the result of a new mutation.

Mitochondrial inheritance

The largest part of human DNA is found in the cell nucleus, with nuclear gene coding. Some DNA is found within mitochondria; here DNA is annular and codes for 13 transcripts. As these transcripts play an important role within the respiratory chain, mutations result in malfunction of organs with a high aerobic metabolism such as the brain, sensory organs and muscles. Mitochondria are passed down over the ovum, which means diseases can only be inherited from the mother and cannot be passed down by the father. Every cell has thousands of mitochondria, but not all of them carry the mutation (heteroplasma), so phenotypes within a family carrying the mutation can vary. Although it is clearly a maternal inheritance, mutations are often difficult to diagnose due to the variance in severity of the disease.
Inheritance and severity of disease

Monogenic diseases with a high rate of new mutations are commonly severe. Patients remain childless in most cases, resulting in the deletion of the mutation from the gene pool. Dominantly inherited diseases with early onset are usually not as severe as autosomal recessive diseases. Autosomal recessive mutations are commonly found in a heterozygote condition within the population. As genetic selection of these recessive mutations can only take place in homozygote patients, it is by far more seldom than genetic selection of dominant genes. Most monogenic inherited diseases are rare within the population as they are genetic exceptions. These diseases are very important from a scientific and diagnostic point of view. A good example is deafness: half of the cases of prelingual deafness have a genetic cause. Analysis points to a defined genetic cause, if the disease follows the model of inheritance of Mendel. These families were ideal examples for genetic coupling analysis and identification of the responsible gene. Another example is deafness within the context of a defined syndrome. These patients differ qualitatively from non-syndromal patients. Identification of genes takes place in the same manner. As the sequence of the human genome is revealed today, one can examine the suspicious gene if a characteristic phenotype occurs and the location of the syndrome is known.

2.2 Complex genetic diseases

As opposed to monogenetic determined diseases, non-monogenetic diseases display certain similarities, but do not follow a specific inheritance. Examples are Diabetes types 1 and 2, hypertension, and presbyacusis. The aetiological aspect of these maladies cannot be itemized phenotypically. Most diseases with a diverse genetic complexity have multiple factors that provide the foundation, implying that the patient possesses a combination of interworking genotypes that induce the disease. However, exogenous influences have to be taken into account as well. The disposition to suffer from a certain disease is inheritable; its manifestation also depends on environmental influences. Diseases with a diverse genetic complexity occur more frequently among relatives in comparison with the common population. Their pattern cannot be assigned to a dominant or recessive inheritance, due to the fact that single components of the genetic disposition profile can be found on different chromosomes and are therefore passed down independently. First-degree relatives of a patient hold some but not all components of the disposition profile. If relatives independently receive single mutations leading to a disposition, they will also be affected. Regarding the collective of patients with a genetically complex disease, such as presbyacusis, part of the cases will be due to exogenous influences such as exposure to noise. From a genetic point of view this is called phaenocopia. Some cases will actually have a monogenetic inheritance. Looking at presbyacusis, one gene might be mutated with a weak functional restraint, whereas a different mutation within the same gene might lead to early hearing impairment.

Aim of research regarding multifactorial diseases

A single mutation or genotype can only explain part of aetiology within a multifactor disease. It is crucial though, to have a closer look at the entire profile of mutations congregated within one patient. At this stage it is impossible to determine a genetic profile for a multifactor disease. Even if all mutations of a disposition profile are known at some point, one is still able to state only the probability for the actual incidence of suffering from the disease. Here, genetic research supports the enlightenment of the pathophysiological paths of diseases. This supports development of new therapeutical targets.

3 Characteristics of genetic diagnostics

Genetic diagnostic differs from usual laboratory diagnostic in multiple ways. Every doctor planning genetic diagnostic should be familiar with these differences.

- Mutations within one gene can have varying results, such as base exchange (missense mutation, stop mutation) or small deletion leading to a shift of the sequence of reading the DNA. The mutation can also result in the deletion or duplication of larger parts of the DNA. It is also possible that changes without functional consequence are detected. Sometimes it is difficult to decide whether the mutation is compatible with the phenotypical consequences. The investigator has to interpret his findings in relation to the methods he used. Even complete sequencing of a gene does not reveal all mutations, as for example, a heterozygote cell will only show the healthy gene, even though the other chromosome might inherit a mutation.
- Conventional laboratory parameters only show a state, which can normalize during the cure of the disease, whereas genetic analysis displays a trait, which is definite. This has to be explained to the patient in detail.
- genetic results can have an impact on relatives
- genetic diagnostic is highly differentiated, so only a specialist having phenotypical information about the patient can decide which gene to investigate.
- A finding analyzed in a genetic laboratory must be interpreted by a consultant, who gives his opinion about the result in the context of an analysis.
4 Indication of genetic diagnostic

As in every laboratory diagnostic, a genetic diagnostic requires proper indication. There are three categories of indication:

• genetic diagnostic in course of differential diagnostic
• predictive genetic diagnostic
• prenatal genetic diagnostic

4.1 Genetic diagnostic in the context of differential diagnosis of a disease

If a certain genetic disease seems possible because of the clinical presentation or the family history, a targeted genetic analysis can support this diagnosis. This is only possible, if the presenting symptoms substantiate the suspicion (e.g., Waardenburg Syndrome). A non-syndromic hearing impairment makes genetic diagnostic very difficult, as there is a high grade of heterogenia.

4.2 Predictive genetic diagnostic

Some genetic diseases commence in the course of life time, such as many types of hearing disabilities. If a patient carries a known disease-inducing mutation, as it is known for autosomal dominant hearing impairments, analysis can identify the mutation in siblings and children of the patient in order to select the risk profile for the disease. This is called predictive genetic diagnostic. If a healthy relative does not carry the disease-inducing mutation, one can conclude that this person will not develop the hearing impairment caused by the mutation. If the mutation is found in the examined person, the chance of developing a hearing impairment depends on the penetrance of the mutation. If the penetrance is high, up to 100%, the predictive genetic analysis has identified a “healthy sick person” or a “sick healthy person”. This can be a strain for the affected person, especially if a cure or prevention doesn’t exist. This is the reason why a detailed consultation is always necessary prior to genetic diagnostic, clarifying the consequences genetic analysis might have. The patient must give consent to the diagnostic procedure.

4.3 Prenatal genetic diagnostic

If a hearing impairment is passed on within a family through autosomal dominant inheritance, children of the patient have a 50% chance of developing the same disease. If the hearing impairment is genetically autosomal recessive, parents are taken by surprise by the disease. The parents are phenotypically healthy, genetically both suffer from the mutation responsible for the hearing disability. They are heterozygote. The risk of passing the disease down to another child represents 25%. If both mutations are localized and analysed, it is possible to perform prenatal genetic diagnostic. Parents seldom make use of this possibility, though, especially regarding autosomal dominant forms of hearing impairment, as these types are not severe, mostly not fully penetrant and commence later in life. If a couple is planning on having prenatal diagnostic, it is again important to clarify the procedure carefully in advance, especially shedding light on the question, which consequences a possible mutation might have for the course of the pregnancy.

5 Genetic diagnostic in otorhinolaryngeal diseases

There are a great number of genetic diseases or syndromes within the speciality of Otorhinolaryngeology, the majority are hearing disabilities. In the following, important examples of every kind of disease will be summarised

5.1 Hereditary hearing disabilities

Hereditary hearing disabilities count among the most common human diseases. As there is great clinical variability, diagnostic is complicated. It is also difficult to identify the mutation causing a certain disease, due to the fact that there is a distinct genetic heterogeneity. The research on hereditary hearing disabilities has considerably contributed to the understanding of hearing and to the molecular structure of the inner ear. Approximately one in 1000 newborns show congenital deafness, half of the cases have a genetic cause (Figure 2). In highly developed countries one can see a decrease of exogene causes for deafness, so the fraction of genetic causes is increasing. The allocation of genetic causes is also demonstrated in Figure 2. Syndromal hearing impairments are characterized by the fact that the hearing disability is part of a super ordinate syndrome, as opposed to an insulated defective hearing, which is then constituted as non-syndromal.

5.1.1 Syndromal types of hereditary defective hearing

There are over 400 known syndromal forms of defective hearing [1]. Here we will illuminate some of the most common forms (Table 1). A syndromal hearing impairment occurs as the consequence of a gene mutation resulting in the malfunction of different organs, such as the dysfunction of potassium transport in Jervell-Lange-Nielsen Syndrome. This malfunction leads to disturbance of conduction in the heart and deafness. The confirmation of the mutation in the gene typical for the syndrome confirms the suspected diagnosis, whereas a missing mutation does not necessarily exclude the existence of the suspected syndrome. It is possible that the mutation is within a non-analysed section of the gene (e.g. part of the intron close to an exon or promoter part). Furthermore the mutation might be within a hitherto unexplored gene. Therefore an otorhinolaryngeologist must always initiate a check-up of other possibly affected organs when suspecting the existence of a syndrome.
Figure 2: Distribution of causes of prelingual deafness [13]

Table 1: Examples for syndromal deafness [1], [13]. SHI = sensorineural hearing impairment; CHL = conductive hearing loss.

| Syndrome                        | Main symptoms                                                                 | Gene            | Inheritance                      |
|---------------------------------|-------------------------------------------------------------------------------|-----------------|----------------------------------|
| Waardenburg-Syndrome I and II   | pigment anomalies, white curl of hair, iris heterochromia; SHI                | PAX3, MITF      | autosomal dominant                |
| Waardenburg-Syndrome IV         | additionally M. Hirschspring (megakolon)                                     | EDNRB, EDN3, SOX10 | autosomal dominant                |
| Stickler-Syndrome 1 and 2       | palatine cleft, spondyloepiphyseal dysplasia, myopia; SHI                     | COL2A1, COL11A1 | autosomal dominant                |
| Stickler-Syndrome 3             | same, but no miopia                                                           | COL11A2         | autosomal dominant                |
| Branchio oto renal (BOR)Syndrome| cysts of the branchial arch, dysplasia of the external ear, preauricular Pits, renal malformation, SHI + CHL | EYA1, SIX1      | autosomal dominant                |
| Usher syndrome type 2A          | retinitis pigmentosa, SHI                                                     | USH2A           | autosomal recessive               |
| Usher Syndrome type 3           | retinitis pigmentosa, vestibular dysfunction, SHI                             | USH3A           | autosomal recessive               |
| Pendred syndrome                | goiter, SHI                                                                   | SLC26A4         | autosomal recessive               |
| Jervell Lange Nielsen syndrome  | prolonged QT-interval in ECG, SHI                                            | KCNQ1, KCNE1    | autosomal recessive               |
| biotinidase deficiency          | seizures, hypotonia, ataxia, psychomotor retardation, impaired vision, alopecia, SHI | BTD             | autosomal recessive               |
| Refsum disease                  | retinitis pigmentosa, neuropathia, ataxia, ichthyosis, SHI                    | PHYH, PEX7      | autosomal recessive               |
| Alport syndrome, autosomal      | glomerulonephritis, hematuria, hypertension, SHI                              | COL4A3, COL4A4  | autosomal recessive autosomal dominant |
| Alport syndrome, X-chromosomal  | glomerulonephritis, hematuria, hypertension, SHI                              | COL4A5          | X-chromosomal                     |
| Mohr Tranebjaerg syndrome       | dystonia, atrophy of the optical nerve, mental retardation, fractures, SHI   | TIMM8A          | X-chromosomal                     |
Table 2: Mitochondrial inheritance: non syndromal deafness [15], [16]

| Gene      | Genetic analysis   | Mutations           | Mutation detection rate | Penetration                        |
|-----------|--------------------|---------------------|-------------------------|-----------------------------------|
| MT-RNR1   | targeted analysis  | 1555A>G, 961deT+(C)\(\pi\) | 21% 50%                 | variable, aminoglykosid induced   |
|           | Sequence analysis  | other mutations     | <1%                     |                                   |
| MT-TS1    | targeted analysis  | 7443A>G, 7444A>G, 7445A>G | 14%                     | variable                          |
|           | Sequence analysis  | other mutations     | 15%                     |                                   |

5.1.2 Non-syndromal, autosomal types of hereditary hearing impairments

Non-syndromal forms of defective hearing are characterized by an extraordinary genetic heterogeneity. Approximately 100 genes, so far partly unexplored, are involved. All three hereditary transmissions can be found: autosomal dominant, autosomal recessive and x-chromosomal. Over 75% of genetic early onset diseases are autosomal recessive and commonly very severe. About 25% of the cases are autosomal dominant and become manifest within early adulthood. These courses of disease can be progressive or non-progressive. Hearing impairment can be limited to certain frequencies. 1–2% of genetic early onset diseases are x-chromosomally inherited. As there is again broad genetic heterogeneity, it can be difficult to identify the mutation. If there is no evidence for a syndromic type of disease, it makes sense to examine the gene coding for connexin-26 (GJP2), as it is a small gene and commonly affected in autosomal recessive disease types. 15–20% of autosomal recessive forms of defective hearing in Germany are due to a mutation of GJP-2. In Mediterranean areas, a certain mutation in the GJP-2 gene (30delG) occurs strikingly often, the frequency of heterozygote being 1:31 [2]. From this one can conclude the frequency of homozygote, which is 1:3800.

Even if the GJP-2 gene carries a homozygote mutation, the grade of hearing impairment can differ. Presumably there are other genes affecting the defect of GJP2-protein with their gene product. There are also rare autosomal dominant mutations within this gene. If no mutation is found in GJP-2, so far no alternative routine method exists to find a mutation in a different gene causing the disease. Consulting large laboratories, which can scan multiple other genes for mutations remains a possibility.

What reasons are there for performing mutation analysis? If parents conceive a child with congenital deafness without a determined cause and with an inconspicuous family history, an autosomal recessive inheritance is very likely. Finding a mutation in the deaf child makes predictive diagnostic in new born siblings possible. This enables the parents to begin adequate therapy right away, if the sibling has the same genotype as the patient. If the disease inducing genotype is excluded in the sibling, no further diagnostic procedures concerning hearing ability are necessary. This applies to other hereditary transmissions including the mitochondrial pathway. Genetic diagnostic can also have a therapeutic impact, as it can be used for early diagnosis of hereditary hearing impairments. Discovering the responsible genetic modification is only successful in a small number of cases. One can expect a progression of diagnostic procedures in the next years, for example kits enabling sequencing for all genes with possible mutations responsible for hearing disabilities.

5.1.3 Mitochondrially coded defective hearing

There are 2 genes in the mitochondrial DNA that lead to a monogen hereditary hearing impairment when mutated (Table 2). In the majority of cases the development of a sensorineural hearing impairment occurs in early adulthood. However, there are also many mild courses of disease, many of which might be due to heteroplasma. Here, a clinical diagnosis is not easy. The penetrance amounts to 80% at 65 years.

Mutations of the MT-RNR1-gene are closely related to aminoglycoside antibiotics, resulting in possible deafness after just a single dose of gentamicin, tobramycin, amikacin, kanamycin or streptomycin. It is important for the ENT doctor to identify the risk profile. If there is suspicion of a maternal inheritance of a hearing impairment, consultation with a professional for human genetics should be initiated, so that mitochondrial coded genes can be analyzed. This indication should be made generously. A MT-RNR1 gene carrier should never undergo aminoglycoside therapy. At risk patients can be identified, as it is characteristically a maternal inheritance. These patients should undergo genetic consultation, giving them insight into possible molecular genetic analysis.

5.1.4 Otosclerosis

Up to 1% of the European population are affected by otosclerosis. A high familiarity has been known for a long time. In spite of intensive research on this disease, so
far there is no definite knowledge of a genetic cause, which would be useful for diagnostic purposes.

5.2 Hereditary malfunction of the olfactory sense – Kallmann Syndrome

The Kallmann syndrome is characterized by a combination of anosmia and hypogonadotropic hypogonadism. Affected men do not develop secondary sexual characteristics, affected women do not develop breasts and suffer from amenorrhea. In addition, kidney agenesis, cheilognathopalatoschisis, brachy- and/or syndactylia or agenesis of the corpus callosum can occur. Clinical presentation of the syndrome is supplemented by diagnosis of laboratory parameters such as decreased hormonal levels (LH, FSH and sexual hormones) and an inconspicuous MRI result of the pituitary gland. The diagnosis is often the result of the physical examination prior to joining the army. The differential diagnosis between Kallmann syndrome and Klinefelt syndrome can be made through an olfactory test. Patients with Klinefelt syndrome have intact olfactory senses. Additionally, they suffer from hyponadotropic hypogonadism. Kallmann syndrome can be caused by mutations in 4 different genes: KS1 through KAL1 on the x-chromosome, KS2 through FGFR1, KS3 through PROKR2, KS4 through PROK2. Whereas KS1 is passed down on the x-chromosome, KS2-4 is inherited in an autosomal dominant transmission. So far proof of mutation is only successful in about 25% of the cases, even when patients present typical clinical features. This is probably due to more unidentified genes responsible for the disease. If Kallmann syndrome is suggested, the ENT doctor should transfer the patient to a geneticist. Other family members are potential carriers of the Kallmann mutation. Hormones should be substituted. With an adequate endocrinological therapy, patients can even reach the state of fertility.

5.3 Tumour diseases

Tumour diseases, especially malignant diseases, depend on genetic state at the cellular level. A cascade of mutations surrounding genes controlling the cell cycle must occur in order to provoke uncontrolled tissue growth. Most tumour diseases are due to somatic mutations and do not have a hereditary genetic cause. Some tumour diseases are hereditary, mostly due to mutations in the germline resulting in mutations in every cell of the embryo. This is a constitutional genetic change. In consequence, hereditary tumour diseases are mutations of tumour suppressor genes, proto-onkogenes or repair genes. The manifestation in organs depends on the tissue-specific expression and cell division activity.

5.3.1 Neurofibromatosis type 2

Neurofibromatosis type 2 (NF2) is characterized by bilateral vestibular schwannoma causing tinnitus, defect of hearing and vertigo [3]. The diseases are passed down in an autosomal dominant hereditary transmission. The approximate age of manifestation is 18–24 years; late onset up into the 70s is also possible. Schwannomas can also occur in other brainstem nerves. Furthermore, other tumour entities such as ependymomas, astrozytomas and meningomas can be found. A posterior subcapsular opacity of the lense is an important clinical feature for diagnosing NF2, although this normally does not influence seeing ability. The clinical diagnosis of NF2 should consider family history. NF2 is due to a mutation in a tumour suppressor gene, severity of the disease depends on the type of mutation [4]. The mutation rate can be as high as 50%. As it is a matter of an autosomal hereditary transmission, the risk of passing down the gene is 50%. Once a mutation is identified, predictive genetic diagnostic can be performed on relatives (Figure 3). Timely detection of mutations allows patients to begin treatment earlier. Patients with a mutation and patients with a high risk profile should have an MRI annually from the age of 12. These patients should undergo a human genetic consultation prior to predictive diagnostic, when the diagnosis of NF2 is suspected.

5.3.2 Paragangliomas

Paragangliomas are a rare familial appearing tumour entity with an autosomal dominant hereditary transmission. These tumours develop in the neck area and are sometimes combined with extra adrenal pheochromocytomas, papillary thyroid gland carcinomas and kidney cell carcinomas [5]. There are two common genes, which can be mutated (SDHB, SDHD). Aberrant from autosomal dominant inheritance transmission, these tumours are exclusively passed down through paternal germ cells. Here, genomic imprinting takes place, meaning that the mutated gene is inactivated during oogenesis [6]. Patients with a suspected familial paraganglioma and their families should submit to human genetic consultation. The diagnostic situation is difficult; predictive genetic diagnostic is possible.

5.4 Congenital syndromes and dysplasias

Organs of the head and neck develop in a complicated ontogenesis, controlled through a large number of genes. The existence of many congenital dysplasias is therefore not surprising. As genes often play important regulatory roles in multiple organic systems, organs can have a congenital malfunction simultaneously. Because this is typical for genetic syndromes, a child with a dysplasia should be scanned carefully for other malformations. As highly specialized medicine now permits, this rule should be carefully followed. Genetic nosology divides diseases into genetic categories, so the human geneticist is accustomed to thinking in terms of the organism and not merely the organ and also regards the patient’s family and not just the patient. In the following we will present examples of syndromes and
dysplasias of the head and neck section. Most congenital dysplasias are not specified or even fully understood genetically. Partly, this is due to the fact that these diseases are very rare. Progress can only be made, when all medical disciplines work together.

5.4.1 CHARGE Syndrome

CHARGE stands for coloboma, heart defect, choanal atresia, retarded growth and development, genital abnormalities and ear abnormalities [7]. Among these symptoms, choanal atresia, dysplasia of the ear conch, hypoor anosmia sensorineural sensorineural or conduction hearing loss, oro-facial clefts and tracheo-esophageal fistulas are within the head and neck specialisation; this can be determined through clinical presentation or through diagnosis. If there is suspicion, molecular genetic examination is possible. CDH7 is the gene known to mutate in about 65% of the cases. The largest amount of cases is due to a dominant new mutation. The disease can be severe in childhood. If the disease is autosomally dominant, it is not as severe and patients can reach adulthood. The grade of dysplasia can vary, even within one family presenting the same mutation.

5.4.2 Franceschetti Syndrome (Dysostosis mandibulofacialis, Treacher-Collins Syndrome)

Franceschetti syndrome is characterized by a hypoplasia of the zygomatic bone and mandibula, by a koloboma and the absence of cilia of the lower palpebra and dysplasia of the ear concha [8]. Half of all patients suffer from a conduction hearing loss due to a dysplasia of the middle ear ossicula. Cheilognathopalatoschisis and choanal atresia can also occur. In representative cases the diagnosis is clinical. The syndrome is passed down in an autosomal dominant transmission, 60% of the cases being due to new mutations. Carriers of the mutation pass the disease to 50% of their children. The genetic cause is a mutation of the TCOF1-gene. A mutation is determined in over 90% of cases.

5.4.3 Holoprosenzephalia

Holoprosenzephalia (HPE) is a structural abnormality of the brain. The prosenzenhalon is not split into two hemispheres. The syndrome can show different stages of severity beginning with lobular forms over semilobular up to alobular holoprosenzephalia. Most patients present with severe ideokinetic retardation, severely affected children die within their first year. Most often patients present with variable kraniofacial dysplasias, such as absence of or a very flat nose, only one nostril, absence of the ossa nasa, defects around the middle in the palatinal bone, uvula bifida, absence of the frenulum of the upper lip or with only a single incisor [9]. Holoprosenzephalia can be part of a chromosomal dysplasia syndrome. It can occur due to dominant new mutations or can also be dominantly inheritable in mild cases. To date there are four identified genes (TGIF, SIX3 and ZIC2),
whose mutation can lead to holoprosencephalia. In addition to mutations, microdeletions can also lead to the disease. The risk of recurrence for children or their relatives is dependent on the cause. Molecular diagnostic is difficult and should remain in experts’ hands.

5.4.4 Branchio oto renal (BOR) Syndrome

The BOR syndrome is characterized by dysplasia of the external-, middle-, and internal ear resulting in both conduction hearing loss and sensorineural hearing loss [10]. Furthermore fistulas and cysts of the pharyngeal arches and dysplasias of the kidneys can be symptoms of the syndrome. The severity of the syndrome varies even within a family. Again, diagnosis is clinical. It is a matter of an autosomal dominant inheritance. A mutation in the EYA1 - gene is detectable in 40% of the cases. Few patients have a mutation in the SIX1-gene. Presumably there are other genes, which have not yet been identified.

5.5 Diseases of the voice and speech

Genetic factors most probably play a role in the development of diseases of the voice and speech, as family and twin analysis suggest. It is most likely that genes controlling the nervous system are the most relevant. It is one of the most fascinating research challenges to fully discover and understand genetic mechanisms and the plasticity of their impact. Our knowledge of these mechanisms is still only fragmentary, so that any practical usage of genetic diagnostics regarding diseases of the voice and speech is not possible.

6 Human genetic consultation – embedding genetic diagnostics in medicine in general

Declaration of a genetic cause for a dysfunction or disease can be very incriminating for the patient as it can result in stigmatization. When a patient’s disease is given a genetic cause, it can often result in the feeling that a judgment has been passed, especially if there is no sufficient therapy or if the symptoms are clearly externally visible as in many genetic syndromes. It is the duty of every doctor to carefully introduce the patient to all technical terms and to explain all biological mechanisms, giving the patient the chance to fully understand the syndrome. Genetic analysis should only be performed if the patient gives his full consent and after clarifying all important facts with the physician. Predictive genetic diagnostic is noteworthy, as it generates “healthy sick” or “sick healthy” patients. The guidelines of the German medical association dictate that genetic diagnostics can only be performed after human genetic consultation and patient consent. Genetic concepts and methods are becoming more and more important in medicine. An interdisciplinary dialogue between doctors of different specialities with the geneticist is mandatory to account for the well-being of each patient and his family.

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Please cite as
Propping P. Genetic analysis for early diagnosis of otorhinolaryngeal diseases. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2008;7:Doc02. DOI: 10.3205/cto000047, URN: urn:nbnd:e:0183-cto0000477

This article is freely available from http://www.egms.de/en/journals/cto/2010-7/cto000047.shtml

Published: 2010-10-07

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