A review on the genetics of otosclerosis

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Background: The aetiology of otosclerosis is not fully understood despite intensive research. It is, however, certain that a genetic component plays a significant role in the manifestation of otosclerosis, although the precise mode of inheritance is still uncertain.
Objective of review: To provide an up-to-date review for the genetics of otosclerosis. The mode of inheritance, chromosomal and linkage studies are presented. In addition, the possible genetic relationship between otosclerosis and osteogenesis imperfecta, and the association between otosclerosis and specific human leucocyte antigen types are described.
Type of review: Systematic analysis of the literature was focused on any information related to the genetics of otosclerosis.
Search strategy: A MEDLINE search (1960–2007) was undertaken to perform a comprehensive review. Articles were also identified through searches of the files of authors.
Results: The majority of epidemiological studies on families with otosclerosis suggest an autosomal dominant mode of inheritance with reduced penetrance of approximately 40%. Genetic linkage studies have demonstrated the presence of six loci (OTSC1, OTSC2, OTSC3, OTSC4, OTSC5 and OTSC7) located on chromosomes 15q, 7q, 6p, 16q, 3q and 6q respectively. Although these loci have been mapped, no causative genes have been identified, and we have little idea of the molecular process involved in this disease. While clinical similarities and some unreplicated genetic association studies suggest an aetiological relationship between otosclerosis and osteogenesis imperfecta-type I, there is no definite evidence of a common pathological process between the two diseases.
Conclusions: Otosclerosis may be considered as a complex disease with relatively common monogenic forms. Knowledge of these genes could lead to substantial improvements in our ability to diagnose and possibly even prevent or treat this type of hearing deterioration.

Otosclerosis is a common, often hereditary disorder, confined to the endochondral layer of the otic capsule of the temporal bone. The disease is characterised by alternating phases of bone resorption and redeposition of new, mainly woven type bony tissue, which has greater cellularity and vascularity than normal bone. Most frequently it involves the stapedio-vestibular joint (oval window), interfering with free motion of the stapes and so causing conductive hearing loss. In some cases, the lesion may spread to involve the cochlea causing sensorineural or mixed hearing loss.[1] Isolated cochlear otosclerosis is rare.[2]

The prevalence of the disease varies in different races. Otosclerosis is more frequently encountered in the Caucasian population with a mean prevalence value of 0.3–0.4% (range 0.2–2%).[3,4] The mean age of onset of clinical otosclerosis is in the third decade; however, some cases begin in early childhood or as late as at 60 years of age.[5] In clinical practice, otosclerosis is more common in females than males, with several studies reporting a female : male ratio of approximately 2 : 1.[6] Further, sex differences in patients with hearing impairment caused by otosclerosis have been reported.[7] Females could have worse bone conduction thresholds and develop a sensorineural component more frequently than that of males.

Despite intensive research by numerous investigators, the aetiology of otosclerosis is still not fully understood. During the last century, a variety of different theories have been postulated to explain the aetiology of otosclerosis, including viral, endocrine, hormonal and autoimmune factors.[5,8,9] It is, however, certain that genetic factors play a significant role in the disease.

The role of heredity in otosclerosis was established in the 19th century when Toynbee[10] first identified the familial nature of the disease. Magnus[11] described a family in which the father and seven of 13 children had conductive hearing impairment, verified in one child to be due to

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ankylosis of the stapes. Hammerschlag[12] and Korner[13] each published pedigrees of families with otosclerosis. Deafness interpreted as otosclerosis, and beginning as early as age of 5 years in some cases, was described by Kabat[14] in 19 members of four generations of a family. The most compelling evidence for the genetic aetiology of otosclerosis comes from a study performed on 40 pairs of monozygotic twins, in which concordance for clinical otosclerosis has been found in nearly all cases.[15]

A detailed review of the literature dealing with the mode of inheritance, chromosomal and linkage studies is presented. In addition, the possible genetic relationship between otosclerosis and osteogenesis imperfecta, and the association between otosclerosis and specific human leucocyte antigens (HLA) types are described.

Method

Type of review

Systematic analysis of the literature was focused on any information related to the genetics of otosclerosis.

Search strategy

A MEDLINE search (1960–2007) was undertaken to perform a comprehensive review. The keywords used included 'otosclerosis', 'otospongiosis', 'genes', 'genetics', 'review', 'linkage analysis', 'chromosome', 'osteogenesis imperfecta' and 'human leucocyte antigens'. These terms were combined in various ways to generate a wide search. Articles were also identified through searches of the files of authors.

Evaluation method

All relevant literature was evaluated by the authors. A glossary for all genetic terms used in this review article is given in Table 1.

Results

Mode of inheritance

Numerous modern studies have shown unequivocally that a genetic component plays a significant role in the disease, although, the precise mode of inheritance is still uncertain. Dominant and recessive, autosomal and sex-linked models and combinations of these have all been proposed.

Autosomal dominant. The majority of epidemiological studies supports an autosomal dominant mode of inheritance with reduced penetrance for familial otosclerosis, a conclusion first reached by Albrecht in 1922.[16] This hypothesis was supported by Larsson[17] who found a positive family history in 80% of reviewed cases. He concluded that autosomal dominant inheritance with penetrance between 25% and 40% accounted for these findings.

Morrison and Bundey[6] conducted a detailed genetic and clinical survey in East London between 1961 and 1964. They investigated a group of 150 otosclerotic patients along with their families and concluded that otosclerosis is an autosomal dominant disease with < 40% penetrance. They suggested that the chance of a child of an affected person being affected is of the order of 25%. Morrison[18] reported many cases of direct transmission through three or four generations and fewer cases with a skipped generation. Further studies on otosclerotic patients and their families performed by Gapany-Gapanavicius[19]and Causse *et al.*[20] suggested that the mode of inheritance best fitted is autosomal dominant with approximately 40% penetrance.

Other modes of inheritance. Alternative modes of inheritance, other than autosomal dominant, are highly unlikely, although could not absolutely be ruled out.[17,19] Bauer and Stein[21] postulated an autosomal recessive mode of inheritance based on a study of 94 families with otosclerotic members. Their work was criticised by Morrison[18] for inadequate otological diagnosis and the apparent inclusion of relatives with deafness of other aetiology. Other authors have suggested a digenic inheritance pattern of otosclerosis. In 1964, Hernandez-Orozco and Courtney,[22] based on a study of 70 probands, postulated two potential interactive genes; one X-linked dominantly inherited gene and one autosomal recessively inherited gene. Of course, as pointed out by Larsson,[23] the mode of inheritance may be different in different families.

There have been some suggestions that otosclerosis may be a polygenic disease.[24] Ben Arab *et al.* performed an analysis in 193 families belonging to 65 pedigrees of otosclerosis.[25] They suggested that the inheritance patterns they observed could best be explained by a polygenic model, in which there was one gene with major effects. They estimated that only 13% of affected patients were carriers of this rare dominant gene, with nearly complete penetrance which varies according to age and sex.[25] The presence of polygenic heredity could explain the variable manifestations of the disease, which does not appear at the same age with the same evolutivity and intensity in all patients.

Sporadic. Although a strong familial component exists, several studies have reported that sporadic otosclerosis represents 40–50% of all clinical cases.[6,19,26] Sabitha

Table 1. Glossary

Allele	One of alternative forms of a gene or DNA sequence occupying a specific chromosomal location
Autosomal dominant	A single, abnormal gene on one of the autosomal chromosomes from either parent can cause the disease
Autosomal recessive	An abnormal gene on one of the autosomal chromosomes from each parent is required to cause the disease
Gene	A functional physical unit of heredity that can be passed from parent to child. All genes in humans are pieces of DNA that contribute to phenotype
Genotype	The genetic constitution of an organism either overall or at specific locus
Heterozygous	An individual who has two different alleles at a specified locus
Homozygous	An individual with identical alleles at a locus
Linkage	The tendency of genes or other DNA sequences to be inherited together as a consequence of their physical proximity on the same chromosome
Linkage analysis	A statistical technique used to identify the location on a chromosome of a given gene involved in a disease relative to the known location of chromosomal markers
Locus	A unique chromosomal region defining the position of an individual gene or other DNA sequence. There may be many candidate genes in each locus
LOD score	A statistical estimate of whether two loci (the sites of genes) are likely to lie near each other on a chromosome and are therefore likely to be inherited together. A LOD score of ≥ 3 is confirmation of linkage, whereas a LOD score <2 excludes linkage
Marker (Genetic)	A segment of DNA with an identifiable physical location on a chromosome whose inheritance can be followed. Markers are often used as tools for tracking the inheritance pattern of a gene that has not yet been identified but whose approximate location is known
Microsatellites	Tandem repeats of a short sequence 2–4 nucleotides in length found at many different locations in the genome
Pedigree	A representation of the ancestral relationship between individuals related genetically or by marriage
Penetrance	The frequency with which a particular genotype manifests itself in the phenotype
Phenotype	The observable characteristics of a cell or organism including the result of any test that is not a direct test of the genotype
Polygenic	A disorder caused by the action of several genes
Polymerase chain reaction	A technique for amplifying a target DNA sequence (by $>10^6$ times) *in vitro* using a DNA polymerase enzyme and primers
Primer	A short oligonucleotide which base-pairs specifically to a target sequence to allow a polymerase to initiate synthesis of a complementary strand

et al.[27] conducted a study involving 153 families in whom 98 (64%) had no history of otosclerosis. This implies that in the majority of patients in their study, the disease was sporadic, as compared with Michael[28] and Ludman[29] who reported only 40–50% and 30% of sporadic cases respectively. The increased proportion of sporadic cases could be due to their inability to screen all the reported 'normal' relatives, as commented by Morrison.[6] It is also possible that a proportion had sub-clinical hearing loss. There appears to be no significant difference in the degree of clinical severity between sporadic and familial cases.

According to Morrison and Bundey,[6] sporadic cases of otosclerosis could arise due to (i) phenocopies (conditions difficult to distinguish from otosclerosis on clinical grounds such as Paget's disease, congenital absence of stapes, von Recklinhausen's disease, rheumatoid arthritis with ossicular joint involvement, osteogenesis imperfecta etc.), (ii) new dominant mutations, (iii) incomplete penetrance in autosomal dominant families and (iv) autosomal recessive or other modes of inheritance including polygenic.

Linkage studies

Conclusive evidence for autosomal dominant inheritance, in at least some families, has lately been provided by the new gene-hunting method of linkage analysis. Linkage analysis is a statistical technique used to identify the location on a chromosome of a given gene involved in a disease by demonstrating a correlation between phenotype and genotype (Fig. 1). The identification of the locus of a gene is the first step towards the identification of the gene itself. The hunt for a locus depends upon affected cases having a high LOD score for a particular locus while controls do not, suggesting that may be the site for the implicated gene. Therefore, large families of cases and controls, as well as clinical confirmation of disease status, are needed for conclusive results.

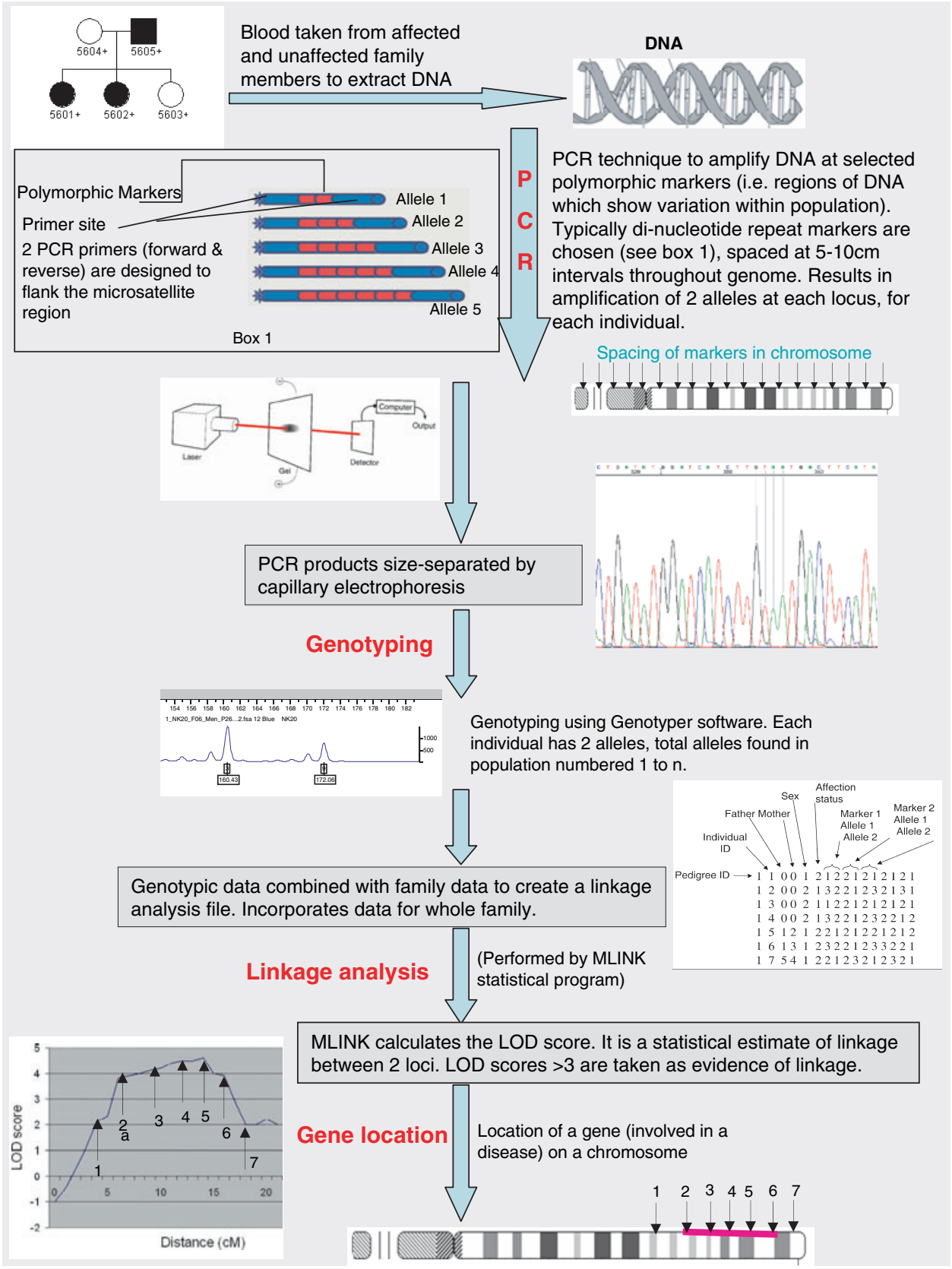

Fig. 1. Schematic presentation of the genetic process followed to identify the location of a gene (from DNA extraction to gene location).

In 1998, Tomek *et al.*[30] were the first to demonstrate genetic linkage in otosclerosis and described the localisation of an otosclerotic gene to chromosome 15q25-q26, named OTSC1. They studied a large multigenerational Indian family with a pedigree indicative of autosomal dominant inheritance. Five out of 16 affected persons had surgically confirmed otosclerosis; the remaining nine had a conductive hearing loss but had not undergone corrective surgery. To locate the disease-causing gene, they performed genetic linkage analysis using markers distributed over the entire genome. This analysis mapped the responsible gene to 14.5 cM region on chromosome 15q26.1 with a peak LOD score of 3.4.[30]

Three years later, a second gene for otosclerosis (OTSC2) located on chromosome 7q34-36, was mapped. Van Den Bogaert *et al.* (2001)[31] completed linkage analysis in a large Belgian family, in which otosclerosis segregated as an autosomal dominant disease. After excluding linkage to the known locus on chromosome 15, they carried out a genome-wide linkage screen and found linkage to chromosome 7q, with a peak multipoint LOD score of 3.54.[31] A year later, the same group performed further linkage studies at the OTSC1 and OTSC2 loci, in additional families.[32] They recruited and analysed nine new families (seven Belgian and two Dutch), with 53 affected and 20 unaffected subjects, so as to investigate the importance of these loci in autosomal dominant otosclerosis. In two families, results compatible with linkage to OTSC2 were found, but in the remaining seven families OTSC1 and OTSC2 were excluded.

Chen *et al.*[33] performed further genome wide linkage studies on a large Cypriot family segregating otosclerosis. Linkage to the known otosclerosis loci on chromosomes 15q and 7q was first excluded. A genome-wide linkage screen identified the OTSC3 locus on chromosome 6p21.3-22.3. The defined OTSC3 interval covers the HLA region, consistent with reported associations between HLA-A/HLA-B antigens and otosclerosis.

In a recent study by Brownstein *et al.*[34], a fourth locus (OTSC4) was identified on chromosome 16q21-23.2 in a large Israeli family of which 12 members had surgically or clinically proven otosclerosis. Linkage to the known otosclerosis loci (OTSC1, OTSC2, OTSC3) was excluded. This analysis mapped the responsible gene to 10.5 cM region on chromosome 16q with a peak LOD score of 3.97. The OTSC4 interval includes several genes involved in the immune system and bone homeostasis that may be good candidates for otosclerosis genes as well.

Van Den Bogaert *et al.*[35] performed further linkage studies in a Dutch family segregating autosomal dominant otosclerosis and a fifth locus (OTSC5) was localised on chromosome 3q22-24. Recombinant individuals delineated a 15.5 cM candidate interval. Statistically significant exclusion of the three known otosclerosis loci (OTSC1, OTSC2 and OTSC3) was also demonstrated in this study.[35]

Table 2. Location of otosclerosis candidate genes

Author	Gene	Location	Interval (cM)
Tomek *et al.*[30]	OTSC 1	15q25-26	14.5
Van Den Bogaert *et al.*[31]	OTSC 2	7q36-36	16.0
Chen *et al.*[33]	OTSC 3	6p21.3-22.3	17.4
Brownstein *et al.*[34]	OTSC 4	16q21-23.2	10.5
Van Den Bogaert *et al.*[35]	OTSC 5	3q22-24	15.5
Thys *et al.*[36]	OTSC7	6q13-16.1	13.4

Recently, a genome-wide linkage study was performed in a large Greek family segregating autosomal dominant otosclerosis. A seventh locus (OTSC7) was localised on chromosome 6q13-16.1 with a peak LOD score of 7.5 – 13.4 cM region.[36] An additional locus, OTSC6, has been reported to the Human Genome Organisation (HUGO) nomenclature committee, but the relevant linkage study has not been published.[36]

Six separate loci were identified in linkage analysis on six large, unrelated and different ethnicity families, thus indicating that otosclerosis is genetically heterogenous (Table 2). Each of these families is atypical in that the penetrance is nearly 100% with approximately half of all individuals in each family being affected. The great majority of families with otosclerosis have too few affected family members to be individually useful in linkage analysis that aimed at mapping new loci.

At present, although six otosclerosis loci on chromosomes 3q, 6p, 6q, 7q, 16q and 15q have been mapped, the responsible genes on these loci have not been cloned. Cloning and completing functional analysis on the causative genes and their related proteins may provide new insights into the molecular mechanisms of otosclerosis and may reveal targets for prevention and treatment of the disease. In all six loci, the defined candidate regions are large. Narrowing of these intervals by the identification of additional families showing linkage would be of great benefit in identifying the responsible genes.

Otosclerosis and osteogenesis imperfecta (type I)

Osteogenesis imperfecta is a genetic disorder of connective tissue caused by an error in type I collagen formation, in either of the two genes, COL1A1 and COL1A2, located on chromosome 17 and 7 respectively.[37] It has autosomal-dominant inheritance with relatively high penetrance.[38]

Osteogenesis imperfecta-type I is characterised by abnormal bone fragility combined with blue sclera and in high percentage of cases (28.7–60%) is associated with impairment of hearing.[39,40] The hearing loss, mainly of conductive type, may occasionally be the result of a fracture or localised dehiscence of the stapedial arch, distal atrophy or absence of the long process of incus, or a fixation of the stapedial footplate.[41,42] In addition to similarities in clinical otological manifestations, the histopathological changes in the ear seen in osteogenesis imperfecta-type I are very similar to those seen in otosclerosis. Therefore, several authors believed that otosclerosis is a local manifestation of osteogenesis imperfecta-type I and that both conditions are possibly based on a common genetic abnormality.[43] The similarities and differences between the two diseases are summarised in Table 3.

Genetic relationship between otosclerosis and osteogenesis imperfecta. Srivastava *et al.*[51] in a study of otosclerosis and type I osteogenesis imperfecta in a family representing three generations concluded that occurrence of otosclerosis and osteogenesis imperfecta in the same family pointed to a common genetic basis in these disorders. Of course, it is possible that this family simply had osteogenesis imperfecta with severe otic involvement, rather than two separate conditions segregating together. There is evidence to suggest that some cases of otosclerosis may be related to defects in expression of the COL1A1 gene, one of the genes that code for type I collagen.[38] McKenna *et al.*[38] investigated the genetic basis of otosclerosis by conducting an association study using polymorphic DNA markers within the COL1A1 gene, from patients with clinical otosclerosis and random control subjects. Their study showed a statistically significant association between clinical otosclerosis and alleles of the COL1A1 gene, suggesting that this gene may play a role in the development of the disease.

In conclusion, while superficial clinical similarities and some unreplicated genetic association studies suggest an aetiological relationship, there is no definite evidence of a common pathological process between osteogenesis imperfecta-type I and otosclerosis. Linkage analysis within large pedigrees, including COL1A1 sequence analysis and COL1A1 allelic expression analysis, would help to clarify the role of this gene in the development of otosclerosis.

Table 3. Similarities and differences between otosclerosis (OS) and osteogenesis imperfecta-type I (OI)

Similarities
Both conditions appear to have an autosomal dominant mode of inheritance[39]
The histopathology of temporal bones from patients with type I OI is similar to that observed in patients with OS. Both characterised by phases of osteoblastic and osteoclastic activity[43]
Half of all patients with type I OI develop hearing loss that is clinically indistinguishable from clinical otosclerosis[44]
Radiological appearances of the otic capsule in OI are similar to severe OS[45]
Similar abnormalities of the non-collagen components of the extracellular matrix have been reported in both OS and OI[46]
Differences
OI involves bones, joints, sclera, teeth and blood vessels whereas similar involvement was not observed in otosclerosis[47]
Optic measurements of the central corneal thickness showed normal values in patients with otosclerosis, while in OI the corneal thickness was significantly reduced[48]
Skin biopsies from patients with otosclerosis and patients with OI revealed reduced dermal thickness in OI, and normal in otosclerosis[48]
Measurements of the bone mineral contents, gave normal results in patients with otosclerosis, while in patients with OI it was significantly reduced[48]
Biochemical studies showed a different enzyme activity pattern between otosclerosis and OI bone samples[49]
Histopathologically there is a greater degree of structural disorganisation and larger resorption spaces in the new bone of OI than in otosclerosis[50]

Association of otosclerosis with HLA system

The correlation of otosclerosis with HLA has received considerable attention in the last decade. HLA is the international designation for the region consisting of the major histocompatibility complex (MHC). This region is located on the short arm of chromosome 6 and consists of the polymorphic genetic system that plays a role in immunological response.[52] The analysis of HLA antigenic determinants of the MHC shows the existence of an association between specific HLA genotypes and several autoimmune diseases. These diseases occur more commonly than expected in subjects with particular HLA phenotypes, which imply that certain HLA determinants may affect disease susceptibility.[53] The antigens encoded by the MHC genes are very heterologous. The differences consist of variations in amino acid sequences reflecting different nucleotide sequences and therefore constitute a tremendous variety of possible gene products. Thus, HLA typing is a useful tool for the study of population genetics.

In view of the genetic nature of otosclerosis and the existence of a number of human diseases in which HLA-linked genes influence susceptibility to disease or to the outcome of the disease, many studies have looked for and found an association between HLA antigens and otosclerosis, but reports are highly variable and these associations have not proven to be consistently reproducible.[54,55] A summary of statistically significant associations of HLA

Table 4. Association of human leucocyte antigen (HLA) and otosclerosis (OS)

Author	Ethnic group	Patients groups		Number of patients		Frequency of a specific HLA types in otosclerosis patients *versus* control subjects	
		Sporadic	Familial	OS	Control	Higher	Lower
Gregoriadis *et al.*[56]	Greek	Yes	Yes	68	400	A11, Bw35 B14	–
Dahlqvist *et al.*[57]	Swedish	Yes	No	74	839	–	B40
Svatko *et al.*[58]	Russian	Yes	Yes	85	113	A2 B12	B40 B27 Cw1
Miyazawa *et al.*[59]	Japanese	Yes	No	62	472	Aw33	–
Bernstein *et al.*[53]	American	Yes	No	49	100	A1, B8 DR3	DR2
Singhal *et al.*[60]	Indian	Yes	No	100	100	A9, A11 B13	–
Gamir *et al.*[61]	Spanish	Yes	No	50	339	HLA-AHLA-B	–
Nibu *et al.*[62]	Japanese	Yes	No	30	220	No association	
Pedersen *et al.*[63]	Danish	Yes	No	100	100	No association	

and otosclerosis are presented in Table 4. HLA antigens may be used as genetic markers to identify hereditary factors associated with a disease. Another purpose of determining an association between HLA and a disease is to define populations that are more susceptible or resistant to disease to understand pathogenesis. Further investigations on larger series of patients in different ethnic groups should be performed to confirm a true association between HLA antigens and otosclerosis.

Key points

- Genetic factors play a significant role in the aetiology of otosclerosis, although the precise mode of inheritance is still uncertain. Most studies on families with otosclerosis support a pattern of autosomal dominant pattern of inheritance with incomplete penetrance of approximately 40%.
- Genetic linkage studies have demonstrated the presence of six loci (OTSC1, OTSC2, OTSC3, OTSC4, OTSC5 and OTSC7) located on chromosomes 15q, 7q, 6p, 16q, 3q and 6q respectively. Although these loci have been mapped, no causative genes have been identified and we have little idea of the molecular process involved in this disease.
- While clinical similarities and some unreplicated genetic association studies suggest an aetiological relationship between otosclerosis and osteogenesis imperfecta-type I, there is no definite evidence of a common pathological process between the two diseases.
- Many studies have described an association between human leucocyte antigen and otosclerosis, but reports are highly variable and these associations have not proven to be consistently reproducible.

Conclusions

Genetic factors play a significant role in the aetiology of otosclerosis. Most studies on families with otosclerosis support a pattern of autosomal dominant pattern of inheritance with incomplete penetrance of approximately 40%, and six otosclerosis loci have been identified, located on chromosomes 15q, 7q, 6p 16q, 3q and 6q.[30,31,33,34,35,36] The causative genes at these loci have not yet been identified and it is not clear whether they will be functionally involved with the pathological processes that have been implicated so far in the disease process. These loci were mapped in large, multigenerational families, which are rather atypical for otosclerosis, so it is not clear whether the same genes will be involved in smaller families and sporadic cases. Identification of the genes involved in otosclerosis will give considerable insights into the cellular pathology of the condition. Besides the traditional positional cloning strategy for monogenic diseases, additional techniques used in complex genetics may be required to identify all of the genes involved in the otosclerosis pathology.

Conflict of Interest

None to declare.

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