Genetics of the Voice

Robert Thayer Sataloff

Department of Otolaryngology, Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.

Summary: Substantial advances have led to the evolution of voice as the newest subspecialty of otolaryngology. Nevertheless, little is known about the genetics of voice. Genetic research is needed to further elucidate the relationship between vocal tract structure (including ultrastructure) and function, mechanisms of voice dysfunction, and transmission of normal and abnormal voice characteristics. Key Words: Voice—Genetics—Heredity.

During the last decade, research discoveries, technological advances, and new clinical insights have resulted in the evolution of a new subspecialty of otolaryngology: voice (1,2). These advances have substantially changed the standard of care for patients with voice disorders, led to sophisticated noninvasive voice therapy, and markedly altered surgical techniques used for voice problems (3). Despite many exciting breakthroughs, much remains to be learned about how the voice functions, what causes phonatory dysfunction, and how voice characteristics (normal and abnormal) are transmitted within families and larger groups. Genetic research has barely begun to address these problems.

GENETICS OF THE VOICE

Genetics of the voice is a fascinating area for speculation and research. Unfortunately, there have been very few studies, and none has been definitive or extensive. In reviewing this subject, a computer search of 8,009,307 references in four databases (MedLine, Health, AidsLine, and CancerLit) was carried out using the following key words: heredity, genetics, voice, voice disorders, and familial. The MedLine database indexes articles from 1966 to present. The computer search produced only five references (4–8), of which only three really discussed hereditary voice disorders (5,6,8). The rest of the conditions discussed in this article were identified through the author's clinical experience and through his review of the content and references contained in numerous speech pathology textbooks and reference texts on human genetics. There appears to be no other published review on the subject of the genetics of voice, although there is a valuable text available on genetic aspects of speech and language (9).

Normal voice

It is clear that genetic factors influence vocal quality. This has been recognized anecdotally in families and even nationalities (Italians, Welsh, Russians, and others). If one assumes that function is related to structure, the association of voice quality and genetic factors is intuitively comfortable. It is generally accepted that physical characteristics are genetically determined. If these include the size of the laryngeal cartilages, vocal fold length and structure, size and shape of the supraglottic vocal tract, and phenotypic similarities elsewhere in the vocal mechanism, then one might expect similarities in voice quality. If we postulate additional similarities in brain development, musical perception, and neuromotor control, the notion becomes even more attractive. However, to be credible, these issues require further study and careful separation of genetic factors from environmental influences upon development.

Some of the most interesting studies to date have
looked at voice function in twins. In general, monozygotic twins have very similar voices. Dizygotic twins appear to show the same differences that would be expected among any children of the same age (10). Coon and Carey (11) studied genetic and environmental determinants of musical ability in twins. Recognizing that there is more to vocal quality and ability than vocal fold structure alone, such studies are of relevance when studying the genetics of voice. Coon and Carey examined monozygotic and dizygotic twins and found evidence of hereditary variation, although environment appeared to be a more important factor than heredity. Kalms and Fry (12) studied dysmelodia (inability to sing on tune) and found it to be inheritable as an autosomal dominant trait with imperfect penetrance. They speculated that their findings seemed to indicate the existence of some deep structure of tonality perception comparable with Chomsky's deep language structure.

Although Bernstein and Schlaper (13) began looking at the genetic influences on the voice as early as 1922, and subsequent work was carried out by Schilling (14,15), Seeman (16), Gedda et al. (17), and others, the complexities of genetic research in humans have left most of the relevant questions unanswered.

Pathological voice and syndromes

In addition to the voice quality characteristics that appear to be transmitted in healthy groups, numerous pathological conditions are associated with specific voice dysfunctions (18). For example, raspy voice quality has been recognized in hyalinosis cutis et mucosae (19-21), Opitz BBB/G compound syndrome (22-25), pachyonychia congenita syndrome (26-28), Werner syndrome (29,30), Williams syndrome (31-34), and other conditions. High-pitched voice occurs in Bloom syndrome (35-38), chondrodystrophic myotonia (39-42), deletion (5p) syndrome (43), Dubowitz syndrome (44-46), Seckel syndrome, Silver–Russell syndrome, and Werner syndrome (29,30). Low-pitched voice has been observed in cutis laxa syndrome (47-49), de Lange syndrome (50-52), deletion (18q) syndrome (53-56), mucopolysaccharidoses (types IH, II, III, VI), and Weaver syndrome (57,58). Other voice abnormalities have been observed in myotonic dystrophy syndrome (18,59) and hereditary dystonias that may be associated with spasmodic dysphonia. A dominant form of spinal muscular atrophy associated with distal muscle atrophy, vocal fold paralysis, and sensorineural hearing loss has been reported. Familial vocal fold dysfunction associated with digital anomalies also exists. Verma et al. (5) described familial male pseudohermaphroditism with female external genitalia, male habitus, and male voice. Urbanova (6) reported familial dysphonia and Friol-Vercelletto et al. (8) reported familial oculopharyngeal muscular dystrophy with associated abnormal voice. Hence, evidence for the existence of a genetic component to vocal quality is compelling.

Molecular genetic considerations

Developments in genetic research in recent years are exciting and have largely moved from clinical to molecular studies. Unfortunately, close scrutiny still reveals discouraging complexities. Much of today's genetic research is involved with gene mapping. This methodology is elegant, but still of limited clinical value for broad questions like vocal quality. In general, at present, genetic markers are useful for conditions associated with one major gene. They require an extremely specific phenotype description. Indeed, linkage studies are extraordinarily difficult and time consuming without specification not only of phenotype, but also of a candidate gene.

Because the basement membrane matrix proteins are found on the long arm of chromosome 1 and other materials may be localized to specific chromosomes, proposal of candidate genes for voice phenomena may actually be practical in selected cases. For example, Mace et al. (60) described a family with hereditary, congenital, bilateral adductor vocal fold paralysis inherited as an autosomal dominant, with linkage with HLA and GLO, a syndrome localized to chromosome 6, position 21.3-23. However, for many questions regarding voice traits and problems, gene mapping is still a cumbersome approach. Undoubtedly, the process will become easier as more of the >100,000 genes in each human genome are mapped and associated with phenotypic expressions. In the meanwhile, it appears as if the most likely avenue of success will be the study of pathological conditions known to be hereditary and associated with voice abnormalities. This research should include genetic, structural, physiological, and epidemiological studies. Such investigations, together with advances in genetic research, should eventually lead us to the kind of information we seek about normal and exceptional voices. Later research efforts are likely to be facilitated by build-
ing a database of pedigree information now. A national registry to coordinate this information may even be appropriate, as suggested by Dr. S. Gray (personal communication). Clinicians should be encouraged to acquire much more meticulous family histories focusing on voice quality, skills, peculiarities, and other nonvoice distinguishing features and diseases. Such clinical research is also likely to provide information that will help clarify the genetic nature of voice traits, not just pathology. In addition, it may give us insight into disease susceptibility. This has been recommended in the past for cancer. However, questions about benign disease still remain to be answered. For example, in families with vocal nodules, we have always assumed environmental factors were causal. Perhaps there are also genetic deficiencies in healing patterns that can be identified. If so, preventive measures may be possible and may guide medical and surgical therapy.

CONCLUSION

Considerable additional study should be encouraged to elucidate the genetics of voice. This research should investigate not only vocal tract structure and function, but also genetic aspects of cortical function, perception, and neurological control, which are inextricably involved in voice production.

Although questions involving heredity are associated with somewhat discouraging difficulties in research design and implementation, they must be addressed along with the more limited anatomical and physiologic questions studied to date. Clinical and molecular genetic research should provide important new insights into healthy and pathological phonation and the relationship between vocal tract structure (such as basement membrane ultrastructure) and function and valuable contributions to the physician’s armamentarium for treating voice disorders.

REFERENCES

4. Rudiger RA, Schmidt W, Loose DA, Passarge E. Severe developmental failure with coarse facial features, distal limb hypoplasia, thickened palmar creases, bifid uvula, and ure-


38. Aberfeld DC, Hinterbuchner LP, Schneider M. Myotonia, dwarfism, diffuse bone disease and unusual ocular and facial abnormalities (a new syndrome). *Brain* 1965;88:313-22.


50. Fraser WI, Campbell BM. A study of six cases of de Lange Amsterdam dwarf syndrome, with special attention to voice, speech and language characteristics. *Dev Med Child Neurol* 1978;20:189-98.


