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Review Synthetic Report

Genomic architecture of deafness in Turkey reflects its rich past

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Abstract - More than 60% of prelingual deafness is genetic in origin, and of these up to 93% are monogenic autosomal recessive traits. Turkey has been continually inhabited since ancient times with traditional settlement of small and isolated villages. There is a high level of both parental consanguinity and assortative mating among the deaf and a long history of the use of sign language. All of these factors are known to have a profound influence on the survival, expression and spread of new mutations for deafness. Many of the identified deafness alleles are private in a single family or in an isolated village that reflect the effect of small population size or parental consanguinity. Single origins have been demonstrated for some mutations, including 35delG in *GJB2* and R84W in *TMIE*, that are recurrently identified in unrelated families. Historic population movements in and around Turkey leading to gene flow and consequently founder effects are responsible for these mutations. Assortative mating among the deaf is likely to have contributed to contemporary high frequency of certain deafness loci.

Key words: Deafness, assortative mating, parental consanguinity, founder effect, Turkey, hearing loss.

Introduction

Hearing loss has many known genetic and environmental causes and affects at least 30% of the population at some time in their lives. Clinically significant hearing loss has been estimated to be present in at least 1.9 per 1,000 infants at birth (Morton and Nance, 2006). Genetic causes of hearing loss are estimated to account for 68% of cases expressed at birth and 55% of those expressed by the age of four. Most genetic changes are monogenic as documented by Morton (Morton, 1991), who estimated that autosomal recessive, dominant, and X-linked genes were responsible for 77%, 22%, and 1% of the genetic cases in western populations, respectively. The prevalence and causes of congenital and profound prelingual deafness can vary widely at different times and among populations. Although studies for genetic epidemiology of congenital deafness began in western populations more than a century ago, comparable studies are few in developing countries. We have recently completed a segregation analysis in Turkey where more than 2,500 families with deafness throughout the country were ascertained with incomplete selection (Tekin and Arici, 2007). Table 1 provides a comparison for the genetic contribution and distribution of genetic causes between the U.S. and Turkey. The high percentage of autosomal recessive deafness appears to reflect the high level of parental consanguinity in the Turkish population. Nevertheless, the proportion of probands arising from deaf by deaf matings (assortative mating) in Turkey is comparable to the Fay data, collected at the turn of the 20th century and the large National Survey conducted in 1969.

Table 1: Segregation analysis of deafness in four surveys of sibships ascertained by truncate selection

Survey (Country, Year)	**Marriages**				**Genetic Deafness**			**Reference**
	Total N	Inbred %	Deaf x Deaf %	Deaf Children N	Total %	AR[1] %	AD[2] %	
E.A. Fay U.S. 1898	2,335	6.8	2.0	3,483	54.9	88.0	12.0	Rose 1975
National U.S. 1969	12,665	0.6	3.3	16,482	50.7	85.6	14.4	Rose 1975
Gallaudet Students U.S. 1973	563	1.4	10.8	749	76.2	77.8	22.2	Rose 1975
National Turkey 2007	2,626	45.2	2.6	3,638	76.8	93.4	6.6	Tekin and Arici 2007

1)AR: Autosomal recessive; 2)AD: Autosomal dominant

Anatolia is an ancient land

Anatolia is a peninsula in the western most part of Asia bounded by the Black Sea to the north, the Aegean Sea to the west, the Mediterranean Sea to the south, and the Caucasus Mountains to the east. It is a part of modern Turkey, which also comprises a piece of land in the eastern part of Europe. Anatolia has played a major role in world history as a bridge connecting East and West. The land was initially occupied by cave dwellers, prior to the emergence of agriculture during the Neolithic period. With the arrival of Assyrian merchants from Mesopotamia, written history was introduced. One of the earliest major empires in the area was that of the Hittites, from the 18th through the 13th century BC. Subsequently, the rulers of Anatolia included the Phrygians, Lydians, Urartus, Greeks, and Turks. The entire area was overrun by the Persians during the 6th and 5th centuries BC and fell to Alexander the Great in 334 BC. The last and most enduring rulers were the Byzantine (330-1453 AD) and Ottoman (1299-1923 AD) Empires.

The very rich and long history of Anatolian settlement makes population admixture inevitable. A Y chromosome haplotype analysis showed that the major haplotypes in Turkey are shared by European and Near Eastern populations. When the frequencies of haplotypes and sub-classes were analyzed, evidence was found for gene flow for both directions between Anatolia and Europe as well as Caucasia (Cinnioglu et al., 2004).

The inhabitants of Anatolia have traditionally lived in small, relatively isolated villages and were often the descendants of a small number of founders migrating from distant lands. Currently, there are approximately 40,000 villages of this type throughout Turkey. Although migration to urban centers has occurred during the past 50 years, the traditional pattern of consanguineous marriage has persisted, and is currently estimated to involve 20-25% of all marriages (Tuncbilek, 2001). However, the rate is as high as 60% in some regions. The combination of the very large number and diverse origins of its founder groups with a high rate of consanguinity has produced an extraordinary spectrum of rare autosomal recessive disorders in Turkey, often associated with different homozygous mutations in individual families (Tuncbilek, 2001).

The most recent support for this claim is our description of a new autosomal recessive form of profound deafness (Tekin et al., 2007; Tekin et al., 2008). The probands in each of five unrelated Turkish families carry different homozygous mutations in the *FGF3* gene. Homozygous *FGF3* mutations associated with the same syndromic findings have subsequently been reported in other populations (Ahmed et al., 2008; Alsmadi et al., 2009).

Records about the presence of a community of deaf individuals serving in the court of the Hittite kings of Anatolia date back at least 3,500 years (Soysal 2001). There are also records about the use of sign language by a deaf community in the Ottoman courts during the 16th and 17th centuries. The first school in modern times for the education of the deaf based on sign language was established in 1889. The number of schools for the deaf in different parts of Anatolia has now increased to 63 within the past 50 years.

Mating structure of the population and its relevance for deafness

Consanguinity and assortative mating are two important characteristics of the mating structure of a population that can have a profound influence on the incidence of deafness. When a new recessive mutation first arises there is a substantial risk that it will be lost by stochastic processes. By facilitating their initial phenotypic expression, inbreeding, resulting either from a small effective population size in a subdivided population or traditional patterns of consanguineous marriage can promote the phenotypic expression and survival of such genes. Once a recessive gene for deafness is expressed in a favorable environment, assortative mating can greatly accelerate the response to relaxed selection. Consanguinity acts on all recessive genes indiscriminately, and its effects are most marked on rare mutations. In contrast, the effect of assortative mating is limited to genes that cause or contribute to deafness where it preferentially increases the frequency of the commonest form of recessive deafness in a population (Nance and Kearsey 2004). Acting together, these two mechanisms can thus promote the survival, expression and spread of genes for deafness.

For example, DFNB3 is a form of recessive deafness caused by a *MYO15A* mutation that has a prevalence of 2% among the 2,385 inhabitants of the village of Bengkala on the island of Bali (Winata et al., 1995), with a carrier frequency of 17% in the hearing population. Remarkably, the inhabitants of Bengkala developed an indigenous sign language, generations ago, which is learned by deaf and hearing villagers alike. Because of their integration into the community, the fitness of the deaf is unimpaired. Deaf by deaf marriages are common, and virtually all are non-complementary (producing only deaf children), as expected, because there is only one form of genetic deafness in the community. Although genetic drift and endogamy undoubtedly played essential roles in the survival and initial phenotypic expression of the *MYO15A* mutation, relaxed selection and assortative mating must also have contributed to the subsequent increase in the frequency of both the gene and the phenotype. Similar examples have been identified among Bedouin tribes where the incidence of deafness can be as high as 2.6% (Palmer et al., 2008), and in the U.S., on Martha's Vineyard (Groce 1985).

We have encountered similar families in Turkey where an indigenous sign language may well have had a positive effect on the survival of genes for deafness throughout human history by creating "negative bottlenecks" or limited periods of time during which the frequency of the most common genes for deafness in the population were amplified by assortative mating and relaxed selection. In addition to sign language, factors promoting such events include large families with multiple affected family members, geographic isolation and the integration of the deaf into the community, which are all present in Turkey (Palmer et al., 2008).

Genetic causes of deafness

Genetic deafness can be classified into syndromic and non-syndromic forms based on the presence or absence of distinctive clinical or laboratory features. More than two-thirds of individuals with deafness have non-syndromic deafness. Examples of non-syndromic deafness are given below.

Connexin deafness (DFNB1)

Because of the large number of recognized genes for deafness, the discovery that mutations at a single locus, DFNB1, account for 30-40% of non-syndromic deafness in many populations, came as a great surprise (Casademont et al., 1997, Zelante et al., 1999). DFNB1 encompasses *GJB2* and *GJB6.* These genes encode homologous connexin 26 (Cx26), and connexin 30 (Cx30) subunits of gap junction proteins that are expressed in the inner ear, and form channels between adjacent cells that permit the exchange of small molecules. At present, more than 150 *GJB2* mutations are known, but a single chain termination mutation, 35delG, accounts for up to 70% of pathologic alleles in many populations. Although DFNB1 is common in Western Europeans and in the Middle East (Denoyelle et al., 1999; Tekin et al., 2003), much lower frequencies in Asian populations have been demonstrated (Liu et al., 2003; RamShankar et al., 2003).

Table 2 shows the frequency of mutations in *GJB2* in 406 probands with deafness from Turkey (Tekin and Arici, 2007). Two large deletions involving the *GJB6* gene were not present in our samples of Turkish probands (Sirmaci et al., 2006). The overall rate of parental consanguinity was 46.8% among all 406 Turkish probands with non-syndromic deafness in whom *GJB2* mutation analysis has been performed. This rate is approximately twice as high as that was reported for the general Turkish population (Tuncbilek et al., 2001). The rate of parental consanguinity increased to 63.2% among multiplex probands with some form of autosomal recessive deafness other than DFNB1. This suggests that many rare forms of autosomal recessive deafness alleles are expressed in the Turkish population.

Table 2: Frequency of *GJB2* deafness by family structure in Turkey

No.of probands	Total Frequency %	Frequency of *GJB2* deafness by mating type				
		Hearing x Hearing				Deaf x Deaf %
		Simplex		Multiplex		
		Outbred %	Inbred %	Outbred %	Inbred %	
406	22.4	20.9	9.3	29.9	18.9	68.8

35delG Mutation in the GJB2 Gene

The 35delG mutation in *GJB2* has been shown to be the most common pathogenic allele in Turkey, similar to the results of studies in Caucasian populations (Tekin et al., 2001; Baris et al., 2001; Bayazit et al., 2003). The 167delT and 235delC mutations are more frequent than 35delG in Ashkenazi Jews (Morell et al., 1998) and in East Asian populations (Yan et al., 2003), respectively. Evidence for single origin was demonstrated for the 167delT mutation in Ashkenazi Jews (Morell et al., 1998) and for the 235delC mutation in East Asians (Yan et al., 2003).

Our studies showed that flanking polymorphic marker alleles are in complete linkage disequilibrium with 35delG, suggesting a single origin in Turkish samples (Tekin et al., 2001; Tekin et al., 2005). The 35delG mutation was reported to have single origin in other populations as well (Van Laer et al., 2001; Belguith et al., 2005). Its approximate age was calculated to be 10,000 years and a presumed founder was proposed to have lived in the Middle East (Van Laer et al., 2001). Based on the high carrier frequency of 35delG in the Mediterranean countries, it was proposed that it arose in ancient Greece (Lucotte and Dieterlen, 2005). Nance and colleagues suggested that the current high prevalence of *GJB2* mutations in many but not all populations is the consequence of relaxed selection and assortative mating (Nance et al., 2000). According to their proposal, the genetic fitness of individuals with deafness must have been very low, possibly approaching zero, in previous millennia. With the discovery that the deaf are educable, the development of sign language, and the establishment of schools for the deaf during the past 2-3 centuries there has been a remarkable improvement in the social, educational, and economic circumstances of the deaf that has been associated with a well documented increase in their fertility (Rose 1975). The spread of sign language and residential schools for the deaf was accompanied by the onset of intense assortative mating among the deaf. This pattern of marriages would be expected to cause a selective amplification of the commonest form of recessive deafness in a population. We have recently provided data in the U.S. that non-complementary matings that can produce only deaf children has increased by a factor of more than five in the past 100 years associated with a statistically significant linear increase in the frequency of pathologic *GJB2* mutations (Arnos et al., 2008).

Other Causes of Non-syndromic Deafness

More than 45 dominant and/or recessive genes for non-syndromic deafness have been identified (hereditary hearing loss homepage - http://webh01.ua.ac.be/hhh/). Most of the 31 genes for recessive hearing loss were initially mapped in consanguineous families or population isolates. Some forms of genetic deafness are quite common either in a single population (Winata et al., 1995) or in many countries (Kenneson et al., 2002), but others still represent isolated observations in which only one affected family has been identified to date (Lynch et al., 1997), and hence little is known about their relative frequency.

Mapping of autosomal recessive Nonsyndromic deafness loci in Turkey

We have screened more than 50 multiplex families with non-syndromic autosomal recessive deafness in Turkey for all known loci using dense single nucleotide polymorphism arrays. Our results indicate that responsible loci are extremely heterogeneous. However, there are recurrent mutations in some relatively common deafness genes.

We have shown that the frequency of *TMIE* mutations is relatively high in Turkey. This is due to a recurrent mutation, R84W, which exhibits a founder effect. We found this mutation in eight of 258 unrelated families with autosomal recessive non-syndromic deafness ascertained from all parts of Turkey. The overall prevalence was 2.4%, but it was higher (10.3%) in Southeastern Turkey (Sirmaci et al., 2009a). We also showed that the haplotypes associated with this mutation are conserved and the mutation was estimated to have arisen about 1,250 years ago, quite likely in the southeastern region of the country (Sirmaci et al., 2009a). Interestingly, in a non-complementary family producing all deaf children, both parents, who were themselves the offspring of unrelated consanguineous parents, were autozygous for two different *TMIE* mutations resulting in affected allozygous children. This pedigree exemplifies the joint effects of assortative mating and consanguinity, and illustrates how the former brings together rare genes for the same trait that may not be identical while the later enhances identity by descent.

Other genes we have sequenced thus far in Turkey do not show striking geographic frequency variation in different regions of Turkey. We found six different mutations, including a 31 kb homozygous deletion in *TMC1,* in seven unrelated families out of 86 from different parts of Anatolia, making its relative frequency 6.6% among the deaf in Turkey (Sirmaci et al., 2009b). We have also identified families with novel recurrent mutations in *MYO15A* and *OTOF*. Other reported families with non-syndromic deafness from Turkey were found to have private homozygous mutations in genes *TMPRSS3* (DFNB8/10) (Wattenhofer et al., 2005), *ESRRB* (DFNB35) (Collin et al., 2008), *PJVK* (DFNB59) (Collin et al., 2007), *LRTOMT* (DFNB63) (Ahmed et al., 2008), and *TMHS* (DFNB67) (Kalay et al., 2006). Clearly gene size is not the only factor that determines the relative frequency of deafness mutations because the most common deafness genes in Turkey, *GJB2* and *TMIE*, are the smallest genes based on their genomic size. Relatively frequent deafness genes typically contain one or more recurrent mutations with founder effects. Population structure and mating type in Anatolia must have promoted their initial survival and enrichment and population movements in the old world leading to gene flow must have played a major role for their spread to different geographic regions.

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