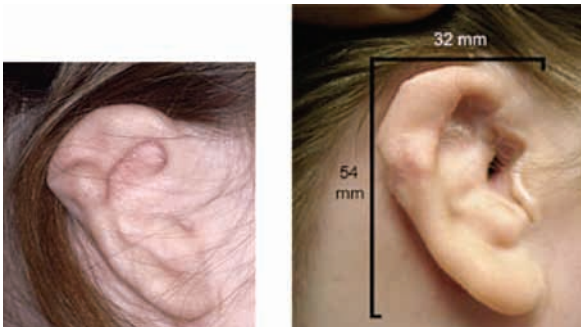
Microtia: "Could Microtia Possibly be Genetic?"

Maria Alexandra Artunduaga, Maria de Lourdes Quintanilla-Dieck and Roland D. Eavey

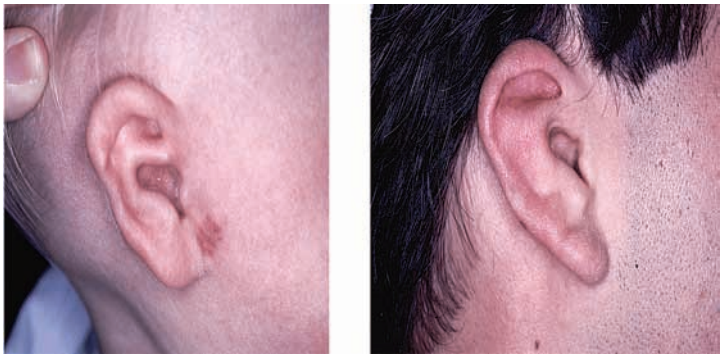
Microtia has remained idiopathic. Most patients have virtually no family members with an ear malformation. Yet two families in my practice have as many as six members with ear malformations – and all ears look different being unilateral, bilateral, typical/severe and moderate in malformation. In **Figure 1** we see one example of an atypical malformation, both pre and post-operatively.

Figure 1. Microtia with aural atresia (pre and post surgery)



In **Figure 2** we see two ears that look similar displaying an unusual configuration of the inner helix curving into the helical root and with aural atresia. But these patients are not related to one another. Could such a similar malformation be genetic if these patients are not related and no family members of each patient have microtia?

Figure 2. Atresia and similar antihelical configuration



We have also seen and tested twin boys with microtia – one twin had left ear severe microtia and the other right ear microtia. In the lab, a 250K SNP array and a comparative genomic hybridization proved the twins to be identical with a mirror image microtia. How might that be possible?

We do know there are environmental causes of microtia, medications can be teratogenic, such as Accutane and Thalidomide. Yet we know also that at times that microtia is genetic such as in Treacher-Collins Syndrome.

So we embarked on a classical twin study [1]. Should a condition be genetic, if Twin A has a specific condition, an identical Twin B will most likely have the condition. If Twin A and B are fraternal twins, and share only 50% of genetic material, the specific condition most likely will appear in one twin only.

We studied 27 sets of twins, and included triplets or quadruplets who could manufactured to be twin sets. We analyzed 32 twin opportunities. We used the heterozygous markers to determine monozygosity or dizygosity. What did we find?

When we compared monozygotic to dizygotic twins - looking for any ear malformation such as a tag, a slightly deformed ear or severe microtia, a large discrepancy was apparent. In identical twins 61% of both twins had an ear malformation. In fraternal twins, only 5% of twins displayed an ear malformation. This was very statistically significant.

Further, the same results held true when analysis of specific severe microtia was evaluated. Therefore, some type of complex genetic interactions influence ear malformations[1].

Monozygotic concordance reveals some type of genetic influence (60%) with some type of environmental influence (40%). That brings up an issue: is this genetic influence a germline mutation – a heritable mutation - with low penetrance? Or is this a spontaneous mutation that happens right after the egg starts to divide? One thing you can do is to look for Copy number Variants (CNVs) and you might be able to tell if it is a *de novo* mutation. This work is on-going in the laboratory.

One possibility for future discovery is the epigenome. As genes are hardware, the epigenome is software and instructs genes whether to express or not to express. In some ways, the epigenome might be more important than the actual genome itself. There are two known mechanisms which enable the epigenetic function. One is with histone proteins, the other is with methylation. The methyl group will grab onto a gene and either allow the gene to express itself or not. Should it be discovered, for example, that a methylation gene, an epigenetic gene, appears at a specific genetic locus, an explanation might be gleaned as to why examination of the phenotype can be so confusing.

References

1. Atrunduaga M, Quintanilla-Dieck M de L, Betensky R, Nicolau Y, Hamdan U, Osorno G, Brent B, Eavey RD, Seidman CE, Seidman JG: A classic twin study of external ear malformations, including microtia. New Eng J Med 2009 Sep17;361(12)1216-121.