GENETICS

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Primary torsion dystonia (PTD) is defined as a syndrome in which dystonia is the only or predominant clinical manifestation, and there is no evidence of neuronal degeneration or an acquired cause. The clinical spectrum of PTD is remarkably broad. Symptoms may begin at any age from early-childhood to the 8th decade and severity ranges from involvement of a single muscle to generalized contractions of the limbs, trunk, neck or facial muscles. When PTD begins in childhood or adolescence, it often starts in a leg or arm, and then progresses over 5-10 years to involve multiple body regions. When PTD begins in adult years, symptoms can first involve the arm (writer's cramp), neck (cervical dystonia or torticollis), laryngeal (spasmodic dysphonia) or eye muscles (blepharospasm). Unlike early-onset, adult or late-onset dystonia tends to remain localized or spreads to an adjacent body region.

PTD is the third most common movement disorder after Parkinson's disease and essential tremor. Adult-onset focal PTD accounts for about 90% of all cases of dystonia with a prevalence estimated at 30/100,000 in the general population. Prevalence estimates for Benign Essential Blepharospasm (BEB) vary between 12 and 133 per million depending on the ethnicity of the study population and the study methodology. BEB is 2.3 times more likely to occur in women than men with a mean age at onset of 56.5 +/- 8.5 which is later than any of the other focal dystonia types.

Seven genes have been mapped for PTD including DYT1, 2, 4, 6, 7, 13 and 17, however, only two of these, DYT1 (TOR1A) and DYT6 (THAP1), have been identified. DYT1, 2, 6, 13 and 17 are associated with an early onset phenotype whereas DYT4 and 7 are more focal in distribution. However, some individulas within early onset families, can manifest with only focal symptoms therefore, the same mutation in an early onset gene can result in both generalized or focal clinical features.

Adult-onset focal PTD is probably more complex genetically than early onset forms and the role of genes as a cause of the various adult clinical subtypes is under study. Several large studies of focal PTD have reported other relatives with dystonia, specifically in cases with BEB, between 9.5%-27% reported a positive family history of dystonia suggesting a strong hereditary component. Most studies suggest the disease is inherited as an autosomal dominant trait, that is, a single altered gene can cause disease, but with a penetrance of between 5-20%, meaning that a person can carry the alteration but does not show any clinical symptoms 80-95% of the time. Only a single large family with BEB has been reported. In this family all known primary dystonia loci were excluded, suggesting the presence of a novel, unmapped gene for blepharospasm which may be associated with higher penetrance. Factors influencing penetrance remain largely unknown. Both genetic and environmental modifiers may play a role. Some of the possible environmental contributors include head trauma with loss of consciousness, prior eye disease or trauma, and dental procedures.

Linkage studies were used to identify the DYT1 and DYT6 genes. In this type of study, large families with multiple affected members are used to identify markers (DNA variations at known location) that co-segregated with the disease in the family. If a marker co-segregates with the disease, this means it is located near (i.e. linked to) the disease gene therefore because the position of the marker is known, the location of the gene is also known. However, because of reduced penetrance, the vast majority of BEB cases appear sporadic or are limited to small families that by themselves are not informative for linkage studies. Instead, association case/control studies represent an alternative method for determining genetic causation. Association studies compare the frequency of variations at a marker, or a set of markers, in unrelated patients (cases) and healthy controls to identify markers that differ significantly between the two groups. Association studies typically identify genes that act as susceptibility factors either increasing or decreasing a person's risk for acquiring a particular disease.

Until recently, most association studies were conducted on candidate genes with one of the most common candidate genes being genes that cause the rare Mendelian forms of the disease. In this same way,

variability, in the form of polymorphisms, in the gene that causes DYT1 dystonia have been examined for their contribution to the risk of developing focal dystonia.

Recent studies implicate polymorphisms (single nucleotide polymorphisms—SNPs) in the DYT1 gene region as being associated with adult-onset, mainly focal dystonia. In cases of focal PTD in the Icelandic population (all types but mainly neck dystonia), a significant association was observed with a group of markers (called a haplotype) spanning the DYT1 gene. However, two studies from Germany using mainly cases with neck dystonia, failed to replicate this association. In contrast, a study involving Italian and North American patients with BEB revealed an association in the Italian group with the same risk allele as was seen in the Icelandic population but no association in the American group. However, when these same two patient groups were stratified based on risk of spread of blepharospasm, both showed a similar association with a SNP in DYT1. Finally, a group of Austrian and German patients with predominantly neck dystonia but including other focal cases, showed a strong association with two other SNPs in the DYT1 gene. But, rather than being a risk haplotype as seen in the previously studied populations, these variants showed a strong protective effect. These contradictory results may be related to several potential problems with these studies including a small sample size (too few patients), too few variations tested across the gene, and a mixture of different subtypes of focal dystonia patients. Nevertheless, the combined results strongly support a role for genetic variability in the *DYT1* gene region as a susceptibility factor in developing adult-onset, focal dystonia including blepharospasm.

With the completion of the human genome project millions of single nucleotide polymorphisms (SNPs) have been identified and mapped to the DNA sequence. Some of these variants contribute to human disease while others may “mark” regions of the genome associated with human disease. Using these resources, association studies no longer have to be carried out on a candidate gene by candidate gene basis where assumptions about the disease cause are used to select the candidates. Instead, a new type of association study using variations across the entire genome can be performed and requires no assumptions about the cause(s) of the disease. This type of study called genome wide association studies (GWAS) offers great potential to identify gene variants that contribute to focal dystonias, however, a large number of cases and controls are needed for these studies. Currently we are conducting a small GWAS in Ashkenazi Jewish patients with BEB as well as other focal dystonias trying to identify associated variations. Because we do not know the number of genes contributing to blepharospasm susceptibility or how large or small their contributions are, we are using samples from a genetically isolated population where the number of genes contributing to the trait are presumably smaller than in the general population. In addition, we presume (based on the DYT1 gene results above) that the different subtypes of focal dystonia will likely share at least some genetic susceptibilities in common, although others may be specific for specific subtypes, and thus have combined samples from patients with different subtypes of dystonia. Eventually, in order to replicate and confirm association findings, we will collaborate with other groups in Europe and the US to combine data from many focal dystonia patients. In this way, the dystonia genetics community should be able to identify genes that contribute to the risk or protection from expressing adult-onset focal dystonia, in general and perhaps, particular subtypes of focal dystonia including BEB. Identification of genetic factors involved in focal dystonia should provide important clues to the mechanisms responsible for the disease and contribute to the development of novel treatments.