The following letter is from Dr. Hodes, explaining their testing.

PMD and mutations in the PLP1 (proteolipid protein 1) gene that cause it.

It is now obvious that changes in the proteolipid protein 1 gene, PLP1, can cause Pelizaeus-Merzbacher disease (PMD) or the closely related condition, X-linked spastic paraplegia (SPG2).

In the 9-10 years since the first mutations were found in boys with PMD, approximately 40 "point" mutations or deletions have been found in as many families. What has been disturbing to the scientists and physicians working with PMD/SPG2 is the fact that somewhere around 80-90% of patients with the disease don't show one of these changes. In the last few years, scientists have discovered that PMD/SPG2 may be caused by a duplication of the proteolipid protein gene.

It is still too early to tell what percentage of PMD/SPG2 is caused by duplications, but a reasonable, ball-park figure would be 50% or more. That still leaves somewhere between 35-50% of patients without a "molecular" diagnosis. Either those patients don't have PMD/SPG2, but a "Pelizaeus-Merzbacher like" disorder, or there are other changes in the PLP gene that we haven’t yet recognized. What about testing for duplications in new families or in families who have not shown a point mutation?

There are two ways to do this, one called a "PCR" (polymerase chain reaction) method and another method that makes use of FISH (fluorescent in situ hybridization). PCR depends on making many copies of the PLP gene and another gene that is not likely to be duplicated, then comparing the ratio of PLP1 to the other gene. A duplicated PLP would double the ratio found in a normal boy. FISH depends on viewing the PLP1 gene directly and looking for two copies. FISH is generally the better method, but in some cases the PCR method is necessary.

We are currently offering FISH and hope to offer both shortly. There are cases in which only one of the methods will provide an answer. Currently, our laboratory is using the following protocol for testing for PMD/SPG2:

- Evaluation of written report of neurological and MRI findings (Drs. Walsh, Edwards-Brown);
- FISH analysis for duplication of PLP1 gene;
- If FISH is negative, sequencing of parts of the PLP1 gene; and
- Consideration of further experiments (examination of RNA, etc).

Edited 4/5/05