EDITORIAL OPEN ACCESS

Splitting vs lumping

Does the phenotype matter anymore?

Steven Pavlakis, MD

Neurol Genet 2020;6:e395. doi:10.1212/NXG.0000000000000395

Correspondence
Dr. Pavlakis
Steven.pavlakis@downstate.edu

RELATED ARTICLE

Delineating *MT-ATP6*-associated disease: From isolated neuropathy to early onset neurodegeneration
Page e393

When we delineated the clinical phenotypes of mitochondrially inherited diseases associated with ragged-red fibers on muscle biopsy in the 1980s, my chairman insisted on defining distinct clinical phenotypes so that in the future, gene finding experiments could be undertaken.[1] We described a distinct clinical entity and named it mitochondrial encephalopathy and lactic acidosis and stroke-like episodes (MELAS). I was a resident writing my second manuscript and found that there were a lot of overlap syndromes. I was not allowed to expand on the concept of indistinct phenotypes. It might muddy the waters and, at a time of new clinical descriptions, might be confusing.

Here, the authors analyzed clinical, genetic, and neuroimaging studies from 132 carriers of a pathogenic MT-ATP6 mutation.[2] The classic syndrome of neuropathy, ataxia, and retinitis pigmentosa (NARP) was described after MELAS and found to be associated with this mutation. In this analysis, the phenotype was extremely variable with age at onset in infancy up to the mid-70s; almost half became symptomatic before their first birthday. The most frequent symptoms were ataxia, progressive encephalopathy, neuropathy, seizures, and retinopathy but only a minority had the classic findings of NARP.

Surprisingly, heteroplasmy was high even in asymptomatic patients. The degree of mutation severity did not predict disease expression and approximately half the patients had a Leigh syndrome phenotype. Oligosymptomatic patients were common in those who presented in adulthood.

So what can we conclude? Heteroplasmy does not predict disease severity in at least this mitochondrial mutation. However, heteroplasmy in the tissue regions has not been looked at systematically. It is possible that heteroplasmy in organs themselves and even in different regions of the brain may play a role in disease expression; as such, the concept of tissue mutation severity cannot be put to rest as a cause of some phenotypic variability.

Furthermore, I do not think we fully understand phenotypic variability at present. Multiple factors both environmental and inherited may play additional roles in disease expression above and beyond the specific pathologic mutation.

But should we abandon the definition of specific phenotypes? Is NARP an important clinical phenotype? I think not so much now, especially when adult onset neuropathy may be caused by this pathologic mutation. Therefore, any symptom that might be associated with mitochondrially inherited disease is sufficient for a genetic evaluation.

Splitting was important at the defining moment of a syndrome. However, with time, the genetic–phenotypic variability is such that specific syndromes are not as clinically relevant as in the past. We have to have a large index of suspicion to look for the pathogenic mitochondrial mutations in patients who may have minimal signs and symptoms. From a research perspective, we understand that phenotypic splitting is still important in gene finding analyses and clinical

From the SUNY Downstate Health Sciences University, Brooklyn, NY.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

trials, so splitting is alive and well at least when looking for new mutations and possibly for treatment trials.

Study funding

No targeted funding reported.

Disclosure

Dr. Pavlakis reports no disclosures. Go to Neurology.org/NG for full disclosures.

Publication history

Received by *Neurology: Genetics* December 2, 2019. Accepted in final form December 18, 2019.

References

1. Pavlakis SG, Phillips PC, DiMauro S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol 1984;16:481–488.
2. Stendel C, Neuhofer S, Floride E, et al. Delineating *MT-ATP6*-associated disease: From isolated neuropathy to early onset neurodegeneration. Neurol Genet 2020;6: e393. doi:10.1212/NXG.0000000000000393.