Mutations in the mitochondrial chaperone *TRAP1* are associated with the triad of chronic fatigue, pain and gut dysmotility: Crazy, criminal, or just caught in the *TRAP*?

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Introduction

Functional disorders such as chronic fatigue syndrome, irritable bowel syndrome, and complex regional pain syndrome are common conditions that often have a substantially negative impact on an individual's well-being. Physicians and other medical personnel often discount these patients, usually with multiple subjective symptoms that are not demonstrable by testing, as being complainers or causing their conditions (e.g. Munchausen). While the etiology of functional disorders is largely unknown, they generally run in families, suggesting a genetic component. As these conditions are common in patients with mitochondrial disease, genes involved with energy metabolism are good candidates in functional disorders pathogenesis.

Through testing of 270 patients, an association between functional disease and variants in *TRAP1* was noted. *TRAP1*, also known as heat shock protein 75 (HSP75) is a mitochondrial chaperone and data suggests it plays a role in antioxidant defense. Like other members of the HSP90, *TRAP1* contains an ATPase domain, which is predicted to be involved in the processing of proteins in an energy-requiring manner. Variants in this domain, particularly I253V, were seen to correlate in patients with functional disease, particularly a triad of chronic pain, chronic fatigue, and gastrointestinal dysmotility.

Methods

This test was designed to sequence the exons and splice sites (+/-10) of every identified (approximately 85%) nuclear encoded mitochondrial gene as listed by MitoCarta (reference) at the time of development. For this test, genomic DNA was extracted from the tissue submitted and captured with an inversion probe method for the genes specific to this panel. This captured target was sequenced on Illumina MiSeq sequencing system with 250bp paired-end reads. Sequence results were mapped to UCSC hg19 genomic reference using Courtagen's proprietary Ziphyr™ bioinformatics pipeline. All variants of interest identified in the "Genetic Variants in Genes Related to Reported Phenotype" were confirmed using di-deoxy (Sanger) sequencing. Sensitivity and specificity for this panel are >99%. Minimum depth of coverage for variant calling is 10X. Identified variants are scored based on the frequency in the general population, evolutionary conservation, and in silico prediction tools (Mutation taster, PolyPhen-2 and SIFT).

Results

- Among the 270 patients referred for sequencing, a significant variant in the *TRAP1* ATPase domain was identified in 12 (4%). Sufficient clinical data was provided for 10 of these patients.
- Three variants within the ATPase domain were identified: I253V, E192K, E216*
- 8/10 experienced a triad of pain, fatigue, and GI dysmotility, compared with 10/95 in our control referral group without *TRAP1* variants experienced this triad ($P = 3x10^{-7}$, OR 34, 95% CI 6-180).
- No *TRAP1* ATPase domain variants were identified among our 50 negative controls.

Table 1: Clinical presentation of 10 subjects with *TRAP1* ATPase domain variants

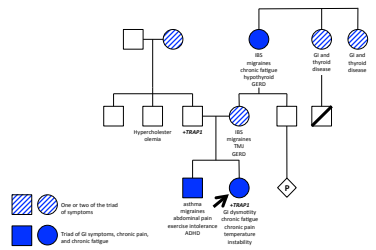
Patient	Variant	Clinical Presentation
1	I253V	**TRIAD**, autism
2	I253V, E192K	**TRIAD**, autism, developmental delay
3	I253V	**TRIAD**
4	I253V	**TRIAD**
5	I253V	**TRIAD**
6	I253V	**TRIAD**
7	I253V	**Pain, fatigue**
8	I253V	**Fatigue, constipation**, Noonan
9	E192K	**TRIAD**, autism
10	E216*	**TRIAD**

TRIAD: The triad includes all of three functional symptoms: chronic pain (including abdominal pain, migraine, etc.), chronic fatigue (including exercise intolerance), and gastrointestinal dysmotility (including gastroparesis and constipation). Other symptoms in blue are part of the triad in patients who did not experience the full triad.

Conclusions

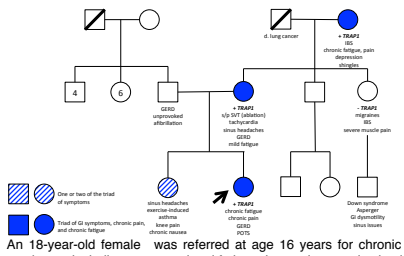
- Sequence variants in the *TRAP1* ATPase domain are correlated with a functional disease triad of chronic pain, chronic fatigue, and gastrointestinal dysmotility.
- While probands generally present with the full triad, the presentation of other family members with the variant varies from non-penetrant or mild functional symptoms to the full triad and/or other clinical, generally dysautonomic symptoms.
- The triad observed in these families appears to arise as a digenomic result of an ATPase domain variant on a permissive mtDNA background. Families with paternally-inherited *TRAP1* variants generally display non-penetrance and/or incomplete presentation of the full triad, although there are exceptions such as the paternal first-cousin in Case 3 below.
- Antioxidant therapy appears to be beneficial, at least for the symptoms of fatigue and pain in these individuals. We are using coenzyme Q10, vitamin C & E, alpha lipoic acid, and N-acetylcysteine.
- We propose the name *TRAP1*-Related Disease (T1ReD), an acronym highlighting which is perhaps the most prevalent and overall troublesome aspect of this disease.
- Many patients and parents of children suffering from functional disease are often passed over in the medical community as mentally ill or attention seeking, often considered to have Muchausen or Munchausen by proxy. By identifying a genetic cause of these often non-specific symptoms, these families can not only obtain a diagnosis that puts an end to their diagnostic odyssey, but may benefit from antioxidant supplementation.

Case 1: I253V



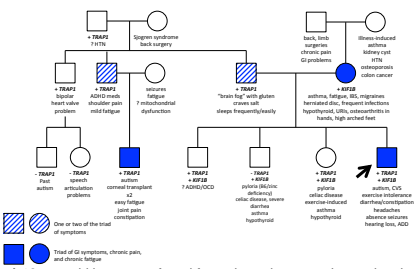
A 4-year-old female was referred at age one year for failure-to-thrive and hypoglycemia. Additional problems include constipation, temperature instability, tachycardia, delayed gastric emptying, almost-daily pain, chronic fatigue, anemia, repetitive episodes of right arm dyskinesia, and neurodevelopmental issues.

Case 2: I253V



An 18-year-old female was referred at age 16 years for chronic fatigue syndrome, including post-exertional fatigue, insomnia, exercise intolerance, and chronic head, muscle, joint, and throat pain. Additional problems include temperature instability, gastrointestinal dysmotility, GERD, gastroparesis, pseudoobstruction, and postural orthostatic tachycardia syndrome.

Case 3: R128H



A 13-year-old boy was referred for autism, absence seizures, hearing loss, attention deficit disorder, ocular apraxia, exercise intolerance, alternating constipation and diarrhea, chronic headaches, cyclic vomiting syndrome, and PANDAS.