Periodic Paralysis and Genetics
"THE RED BADGE OF COURAGE"

By Susan Q. Knittle-Hunter

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Day after day people with Periodic Paralysis contact me on the Periodic Paralysis Network. Most every story is the same. Each one has periods of paralysis due to potassium shifting. They are very ill with varying degrees of permanent muscle weakness and problems breathing. They have had the symptoms as long as they can remember but they are unable to get a clinical diagnosis due to the attitudes and lack of proper education of their doctors. These people are unable to get the medical help they need and are seeking support and information. Most have broken spirits and have lost everything including careers, family and friends.

There is another group who contacts me. These people also have periods of paralysis due to potassium shifting. They are very ill with varying degrees of permanent muscle weakness and problems breathing. They have had the symptoms as long as they can remember but they have a clinical diagnosis. This means they are diagnosed based on their symptoms; however, they have not been diagnosed genetically. The genetic mutation, the basis for their symptoms, has not been found yet.

These people are either unable to join some of the Periodic Paralysis boards, listservs or social groups on the internet, or if they are allowed to join, they are treated rudely or ignored. This is done by the other members and by the doctors who "lurk" on these boards.

It seems that if one does not have an identified genetic mutation, he or she does not "really" have Periodic Paralysis. His or her periodic paralysis episodes and potassium shifting and other symptoms and suffering are somehow not as equal as those who have a genetic marker.

Men and women without genetic markers are just as ill, if not more ill because they have gone untreated for many years and need treatment just as much as those that do have markers. Most of them are in dire need of support and help. That is why they join these boards.

What is happening to them is unconscionable. I know because I was one of them. On several occasions I desperately needed help. I asked specifically if one of the doctors could please answer my "life and death" questions about when to call

911 based on potassium levels and symptoms. I never heard back from any doctor and only a few members in my own situation responded. On other occasions members actually challenged me on issues or questions I asked. I sunk into deep despair after months of this, especially when I noticed that when the possibility of a doctor appearing on a TV show was discussed, a doctor was responding on the listserv within a few minutes of the post, wanting information about it. Apparently, being on TV was more important than helping sick people.

It was clear that the people who were ill and needed help were not getting it nor were they going to on those boards. It was also clear that a divisive distinction was set up between the "haves" and the "have-nots". This is part of the reason we created the Period Paralysis Network.

One morning after hearing about a conversation on a Periodic Paralysis board, about the genetic markers, I became fed up. Apparently, a woman was unable to get a genetic diagnosis based on the fact that a doctor would not do it because he would be "stepping on the toes" of another genetic researcher and the basis of the decision was research money. Without the diagnosis, the woman was unable to get the medications and treatment she and other family members needed. I wrote this following note to my friend who was still a member and being abused daily. Her genetic mutation has not been found yet although her blood had been sent to the genetic specialist four years ago.

> *I want this madness to stop...so I am just going to make a small comment or two....* ***To all of the doctors involved and the others with PP who wear their mutation numbers as a "badge of honor"****:....bottom line....****who gives a flying f$&k.?****....We are all sick with varying degrees of periodic paralysis, some of us are dying...get over it doctors and forget the genetic mutation....****TREAT US****...****we need help****.....In MD, MS, ALS, Cancer, etc does anyone have to have a genetic test before they are treated? Others wear their "badge of honor" while the rest of us must wear a scarlet letter...either, "H" for hypochondriac. "F' for faker, "M" for malingerer or "C" for conversion disorder. We also have another badge posted on our back that must say "KICK ME", especially when I am down. But what most of us has to wear is a* ***RED BADGE OF COURAGE*** *to face the message boards, doctors and our families everyday...Please stop this madness.....*
> *You may quote me on this.....Susan Q. Knittle-Hunter*

The following is the truth about the genetic mutations for Periodic Paralysis and Andersen-Tawil Syndrome:

Specifics for Genetic Diagnosing of Periodic Paralysis

"Genetic testing is being used for research, but it is not yet reliable enough to be entirely relied upon for diagnostic purposes. While a positive genetic test can prove your patient has HypoKPP, a negative result does NOT rule out the possibility of HypoKPP. While eleven **mutations have been identified the commercial genetic labs currently only offer tests for the** three **most common mutations. There are also other mutations yet to be identified. So far genetic tests can identify about 30-70 out of 100 of positively diagnosed patients, which means that a substantial number of patients have genetic variants which have yet to be identified."**

http://hkpp.org/physicians/dxing_hypokpp.html

"The most definitive way to make the diagnosis is to identify one of the calcium channel gene mutations or sodium channel gene mutations known to cause the disease. However, known mutations are found in only 70% of people with hypokalemic periodic paralysis (60% have known calcium channel mutations and 10% have known sodium channel mutations). This situation will improve as further mutations are identified. In the meantime, if potassium helps relieve or prevent episodes, this fits with hypokalemic periodic paralysis."

"Among the 30% of people who appear to have hypokalemic periodic paralysis but don't have mutations in the two genes known to cause hypokalemic periodic paralysis the following are often noted:

- **Migraines**
- **Heart rhythm abnormalities**
- **Attention deficit disorder (ADD, ADHD)**
- **Relative insensitivity to the local anesthetic lidocaine and "dental anxiety"**
- **Severe premenstrual syndrome (PMS)"**

http://simulconsult.com/resources/hypopp.html

A link to a good article about diagnosing Periodic Paralysis:

http://emedicine.medscape.com/article/1171678-diagnosis

Specifics for Genetic Diagnosing of Andersen-Tawil Syndrome

I have sited a few articles below, which explain this.

How Common Is It?

Andersen-Tawil syndrome is a rare genetic disorder; its incidence is unknown. About 100 people with this condition have been reported worldwide.
Type 1 accounts for about 70% of all cases of Andersen-Tawil syndrome.
Type 2 accounts for the remaining 30% of cases of Andersen-Tawil syndrome.

Genetics & Inheritance

Andersen-Tawil syndrome type 1 is caused by mutations in the KCNJ2 gene. The cause of cases of Anderson-Tawil syndrome type 2 is unknown.

http://www.inheritedhealth.com/condition/Andersen-Tawil_Syndrome/37

ATS is caused by missense mutations or small deletions (Plaster *et al*., 2001; Tristani-Firouzi *et al*., 2002; Ai *et al*., 2002; Andelfinger *et al*., 2002; Donaldson *et al*., 2003; Hosaka *et al*., 2003) in *KCNJ2*, encoding the inwardly rectifying K channel, Kir 2.1 (Plaster *et al*., 2001), in approximately two-thirds of the affected individuals (ATS1) (Plaster *et al*., 2001; Tristani-Firouzi *et al*., 2002; Donaldson *et al*., 2003). The molecular lesion(s) have not been identified in ~ 30% of subjects including kindreds not linked to *KCNJ2*.

http://brain.oxfordjournals.org/content/129/1/8.full

The following is the criteria for making a clinical diagnosis:

Table 3 Diagnostic criteria for ATS

(1) A clinically definite diagnosis requires two of the following three features:

a. PP
b. Prolonged QTc interval or ventricular ectopy (identified on ECG or Holter)
c. The typical ATS facies including:
Low set ears, ocular hypertelorism, small mandible, fifth digit clinodactyly, syndactyly

(2) Alternatively, a diagnosis may be made with one of the three features above and an affected family member meeting two of three.

http://brain.oxfordjournals.org/content/129/1/8.full.pdf

Based on the above criteria, I was diagnosed by meeting a, b and c. Therefore, my relatives could be diagnosed based on a, b or c and my diagnosis.

In a paper written by and just updated by Dr Rabi Tawil himself, it is stated that Type 1

and Type 2 are indistinguishable in how they are manifested. They can't find any difference in people with Type 1 or Type 2. The cause is the difference; in Type 1 the cause is known, in Type 2 the cause has not yet been found.

Here is the research:

Periodic Paralysis: Andersen-Tawil Syndrome Type 2

Type 1 and type 2

Two types of Andersen–Tawil syndrome are distinguished by their genetic causes.

- Type 1, which accounts for about 60 percent of all cases of the disorder, is caused by mutations in the *KCNJ2* gene.[1][2]
- The remaining 40 percent of cases are designated as type 2; the cause of the condition in these cases is unknown.

The protein made by the *KCNJ2* gene forms a channel that transports potassium ions into muscle cells. The movement of potassium ions through these channels is critical for maintaining the normal functions of skeletal muscles which are used for movement and cardiac muscle. Mutations in the *KCNJ2* gene alter the usual structure and function of potassium channels or prevent the channels from being inserted correctly into the cell membrane. Many mutations prevent a molecule called PIP2 from binding to the channels and effectively regulating their activity. These changes disrupt the flow of potassium ions in skeletal and cardiac muscle, leading to the periodic paralysis and irregular heart rhythm characteristic of Andersen–Tawil syndrome.

Researchers have not yet determined the role of the KCNJ2 gene in bone development, and it is not known how mutations in the gene lead to the developmental abnormalities often found in Andersen–Tawil syndrome.

http://en.wikipedia.org/wiki/Andersen-Tawil_syndrome#Type_1_and_type_2

Molecular Genetic Testing (Written by Dr Tawil himself)

Andersen-Tawil Syndrome

LQT7, Long QT Syndrome 7, Andersen Syndrome. Includes: Andersen Syndrome Type 1, Andersen Syndrome Type 2

Rabi Tawil, MD
Department of Neurology
University of Rochester Medical Center
Rochester, NY
rabi_tawil@urmc.rochester.edu
Shannon L Venance, MD, PhD
Department of Clinical Neurological Sciences
London Health Sciences Centre
University of Western Ontario
London, Ontario
shannon.venance@lhsc.on.ca

Initial Posting: November 22, 2004; Last Update: May 13, 2010.

"Gene. *KCNJ2*, encoding the inward rectifier potassium channel 2 protein (Kir2.1), is the only gene known to be associated with Andersen-Tawil syndrome type 1 (ATS1).

Other loci. To date, no other loci have been identified to account for ATS (termed Andersen-

Tawil syndrome type 2, or ATS2) in the 40% of kindreds not linked to *KCNJ2*."

Genotype-Phenotype Correlations

Individuals with clinically defined ATS are phenotypically indistinguishable, regardless of the presence of a *KCNJ2* mutation (ATS1) or absence of a *KCNJ2* mutation (ATS2) [Tristani-Firouzi et al 2002, Donaldson et al 2003].

In a single large kindred with the *KCNJ2* Arg67Trp mutation, periodic paralysis was observed only in men, cardiac symptoms only in women, and congenital anomalies in both [Andelfinger et al 2002]. However, this apparent sex-limited bias in clinical presentation has not been confirmed [Donaldson et al 2003, Davies et al 2005]. "

http://www.ncbi.nlm.nih.gov/books/NBK1264/

Specifics for Genetic Diagnosing of: Hypokalemic Periodic Paralysis and Hyperkalemic Periodic Paralysis

Molecular Genetic Testing

Genes. Two genes are known to be associated with hypokalemic periodic paralysis (HOKPP):

- ***CACNA1S*,** accounting for approximately 55%-70% of HOKPP
- ***SCN4A*,** accounting for approximately 8%-10% of HOKPP

Other loci. One study suggested that mutations in another potassium channel gene, *KCNE3*, cause HOKPP [Abbott et al 2001] and thyrotoxic periodic paralysis [Dias Da Silva et al 2002a]; however, two further studies did not support this hypothesis, showing that this missense variant is present in 0.8%-1.5% of the healthy population [Sternberg et al 2003, Jurkat-Rott & Lehmann-Horn 2004].

The nine most common mutations in *CACNA1S* and *SCN4A* do not account for about 20%-36% of individuals with clinically diagnosed HOKPP, indicating possible further allelic heterogeneity and/or genetic heterogeneity of the disorder [Sternberg et al 2001, Miller et al 2004]; however, no other loci have been identified.

Clinical testing

- ***CACNA1S* (hypokalemic periodic paralysis type 1)**

  Targeted mutation analysis. Four mutations (p.Arg528His, p.Arg1239His, p.Arg1239Gly, p.Arg528Gly), clustered in exons 11 and 30, are present in approximately 55%-70% of individuals with HOKPP [Jurkat-Rott et al 1994, Ptacek et al 1994a, Sternberg et al 2001, Miller et al 2004, Wang et al 2005]. Mutations p.Arg528His and p.Arg1239His are far more common than p.Arg1239Gly and p.Arg528Gly. A fifth mutation in exon 21 (p.Arg897Ser) has been described recently [Chabrier et al 2008].

  Sequence analysis of select exons. Alternately, exons 11 and 30 can be analyzed by direct sequencing, which detects the four common mutations and any additional sequence variants in these exons. Sequencing of exon 21 should also be performed [Chabrier et al 2008].

Sequence analysis **of entire** **coding region** is also available on a clinical basis and may be considered when targeted mutation analysis or sequencing of select exons is negative (see Testing Strategy).

- ***SCN4A*** **(hypokalemic periodic paralysis type 2)**

Sequence analysis **of select** **exon(s).** Sequence analysis of exon 12 detects five mutations (p.Arg669His, p.Arg672Ser, p.Arg672His, p.Arg672Gly, p.Arg672Cys) that account for approximately 10% of individuals with HOKPP [Bulman et al 1999, Jurkat-Rott et al 2000b, Sternberg et al 2001, Bendahhou et al 2001, Davies et al 2001, Kim et al 2004]. Sequence analysis of exon 18, in which a sixth mutation (p.Arg1132Gln) has been described, should also be performed [Carle et al 2006].

Sequence analysis / **mutation scanning** **of entire** **coding region** of *SCN4A* may detect rare or *de novo* mutations, such as the one reported by Sugiura et al [2000] in a family with a combination of heat-induced myotonia and cold-induced paralysis.

Table 1. Summary of Molecular Genetic Testing Used in Hypokalemic Periodic Paralysis

Gene Symbol	Test Method	Mutations Detected	Proportion of HOKPP Diagnosed with This Test Method	Test Availability
CACNA1S	Targeted mutation analysis	p.Arg528His, p.Arg1239His, p.Arg1239Gly, p.Arg528Gly p.Arg897Ser [1]	55%-70%	Clinical Testing
	Sequence analysis of exons 11, 21 and 30 [2]	Sequence variants	55%-70%	
	Sequence analysis of entire coding region	Sequence variants	Unknown	
SCN4A	Targeted mutation analysis	p.Arg669His, p.Arg672Ser, p.Arg672His, p.Arg672Gly, p.Arg672Cys p.Arg1132Gln [3]	8%-10%	Clinical Testing
	Sequence analysis exon 12 and 18	Sequence variants [3]	8%-10%	
	Sequence analysis of entire coding region	Sequence variants	Unknown	

Test Availability refers to availability in the GeneTests Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. Mutations tested may vary among laboratories.
2. Exons sequenced may vary among laboratories.
3. Includes, but not limited to, detection of variants p.Arg669His, p.Arg672Ser, p.Arg672His, p.Arg672Gly, p.Arg672Cys, p.Arg1132Gln. Mutations detected may vary between laboratories.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirming the diagnosis in a **proband.** One approach to molecular genetic testing is the following:

1.

Test for common mutations in exons 11 and 30 of *CACNA1S* by targeted mutation analysis or sequencing of select exons.

2. If no mutation is identified, sequence exon 12 and 18 of *SCN4A* and exon 21 of *CACNA1S.*

3. If no mutation is identified, sequence all coding regions of *SCN4A* to search for mutations associated with normokalemic and hyperkalemic periodic paralysis (in case the diagnosis of HOKPP is incorrect).

4. If no mutation is identified, sequence all coding regions of *CACNA1S* in search of a novel/rare mutation.

5. If no mutation is identified, sequence the coding region of *KCNJ2* for a mutation that could cause Andersen-Tawil syndrome, which can mimic HOKPP.

Predictive testing for at-risk asymptomatic family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

CACNA1S. While missense mutations in exons 11 and 30 can cause HOKPP type 1, missense mutations in exon 26 (p.Arg1086Cys, p.Arg1086His) have been shown to cause autosomal dominant malignant hyperthermia susceptibility (MHS) without HOKPP in at least two families [Monnier et al 1997, Jurkat-Rott et al 2000a]. One family with combined HOKPP and MHS caused by an unidentified mutation has been reported [Rajabally & El Lahawi 2002]. Mutations in the *CACNA1S* gene account for 1% of all individuals with MHS [Stewart et al 2001].

MHS is a pharmacogenetic disorder of skeletal muscle calcium regulation. MH-susceptible individuals respond to volatile anesthetics (halothane, sevoflurane, desflurane, enflurane, isoflurane) or depolarizing muscle relaxants (succinylcholine) with uncontrolled skeletal muscle hypermetabolism. The triggering substances release calcium stores from the sarcoplasmic reticulum, causing contracture of skeletal muscles, glycogenolysis, and increased cell metabolism, resulting in production of heat and excess lactate. Affected individuals experience acidosis, hypercapnia, hypoxemia, rhabdomyolysis with subsequent increase in serum creatine kinase (CK) concentration, hyperkalemia with a risk of cardiac arrhythmia or even arrest, and myoglobinuria with a risk of renal failure. In almost all cases, the first manifestations of MH occur in the operating room. Death results unless the individual is promptly treated.

SCN4A. While missense mutations in exon 12 cause HOKPP type 2, a large number of missense mutations in other exons have been shown to cause autosomal dominant disorders characterized by hyperexcitability of the sarcoplasmic membrane [Ptacek et al 1991, Rojas et al 1991, Plassart et al 1994, Ptacek et al 1994b]:

- **Hyperkalemic periodic paralysis type 1 (HyperPP1).** HyperPP1 is characterized by: attacks of flaccid limb weakness (possibly including muscle weakness of the eyes, throat, and trunk as well); hyperkalemia (>5 mmol/L) or an increase of serum potassium concentration of at least 1.5 mmol/L during an attack of weakness and/or provoking/worsening of an attack by oral potassium intake; normal serum potassium and muscle strength between attacks; onset before age 20 years; and absence of paramyotonia (muscle stiffness

aggravated by cold and exercise). The attacks of flaccid muscle weakness usually begin in the first decade of life. Initially infrequent, the attacks increase in frequency and severity over time until approximately age 50 years, after which the frequency declines considerably.

Potassium-rich food or rest after exercise may precipitate an attack. A cold environment, emotional stress, glucocorticoids, and pregnancy provoke or worsen the attacks. A spontaneous attack commonly starts in the morning before breakfast, lasts for 15 minutes to an hour, and then disappears. Usually, cardiac arrhythmia and respiratory insufficiency do not occur during the attacks.

Between attacks, HyperPP1 is usually associated with mild myotonia (muscle stiffness) that does not impede voluntary movements. Many older individuals with HyperPP1 develop a chronic progressive myopathy.

- **Paramyotonia congenita (PC).** PC in general is characterized by myotonic symptoms followed by weakness; symptoms are worsened by repeated movements and triggered or aggravated by exposure to cold [Plassart et al 1994, Ptacek et al 1994b]. It is caused mainly by mutations at codons 1313 and 1448 of *SCN4A*.
- **Potassium-aggravated myotonias (PAM) and related disorders.** This group of diseases is characterized by myotonic symptoms that are neither clearly ameliorated by exercise (as in myotonia congenita) nor worsened by exercise and cold (as in paramyotonia congenita). Symptoms may fluctuate (myotonia fluctuans) or be permanent (myotonia permanens) and/or be aggravated by potassium. They may respond to acetazolamide (acetazolamide-responsive myotonias) [Trudell et al 1987]. PAM and related disorders are caused mainly by mutations at codon 1306 of *SCN4A*. These myotonic syndromes are distinct from myotonic dystrophy type 1 (DM1), caused by a trinucleotide repeat expansion in *DMPK*, and myotonic dystrophy type 2 (DM2), also called proximal myotonic myopathy (PROMM), caused by a tetranucleotide repeat expansion in *ZNF9*.

  Diseases caused by mutations in *SCN4A* may also be intermediate or compound forms of HyperPP and PC, or PC and PAM.
- **Malignant hyperthermia susceptibility**. Moslehi et al [1998] described a large kindred in which affected individuals had hyperkalemic periodic paralysis with or without MHS. None had MHS alone. The causative *SCN4A* allele was later characterized as having a double mutation, p.[Phe1490Leu + Met1493Ile] [Bendahhou et al 2000]. Vita et al [1995] described a kindred with succinylcholine-induced masseter muscle rigidity, a complication of anesthesia other than malignant hyperthermia susceptibility that was caused by a missense mutation of *SCN4A*, p.Gly1306Ala.

http://www.ncbi.nlm.nih.gov/books/NBK1338/