GENETICS IN HEREDITARY NEUROPATHY

ERNESTO ALONSO, SWETHA JASTI,MAZEN M.DIMACHKIE, RICHARD J. BAROHN, MELANIE GLENN, OMAR JAWDAT, JEFFREY STATLAND, LAURA HERBELIN, CONSTANTINE FARMAKIDIS,DUAA JABARI, MAMATHA PASNOOR

40 ANNUAL CARELL-KRUSSEN NEUROMUSCULAR SYMPOSIUM, DALLAS, TEXAS

FEBRUARY 23, 2018

Background

Hereditary neuropathies are a large group of genetically and phenotypically heterogeneous disorders, categorized by involvement of motor, sensory and or autonomic nerves (Dyck, 2005)

Divided in 3 categories

- Hereditary motor and sensory neuropathies (HMSN) also known CMT
- Hereditary motor neuropathies (HMN)
- Hereditary sensory and autonomic neuropathies (HSAN)

Diagnosis is established based on history and clinical assessment

About seventy genes have been described in the literature to cause inherited neuropathies (Rossor, 2013)

Inheritance : autosomal dominant, autosomal recessive, X-linked inheritance patterns, sporadic

Background

A genetic diagnosis is identified in

- 50-70% of Charcot-Marie-Tooth disease (Vallat , 2013) patients
- 30% of hereditary sensory and autonomic neuropathy (HSAN) (Rotthier, 2012)
- 20% of distal motor neuropathy (Rossor, 2012)

With increasing availability of genetic testing new mutations are being identified with associated clinical phenotypes

- PMP22 deletions cause 80 % of HNPP cases
- PMP22 duplications cause 70 % of CMT 1 cases
- Pathogenic mutations in some genes have been associated with multiple phenotypes or clinical patterns (eg mutations in GARS gene can be associated with Charcot-MarieTooth type 2D or with distal SMA type V)

Objectives /Study Design

- **Objective**
  - **To review the genetic mutations identified in patients with suspected hereditary neuropathy at KUMC**
  - **Associate with the clinical phenotypes**

- **Study Design: Retrospective chart review**

Methods

- IRB approval for exempt status was obtained
- A retrospective chart review was performed of patients with suspected hereditary neuropathy with genetic testing performed between January 2013 to December 2017
- 100 charts were reviewed to date
- Information was collected on the demographics, clinical findings, laboratory data, electro diagnostic testing and genetic testing results
- Data obtained based on available free genetic testing through Alynlam

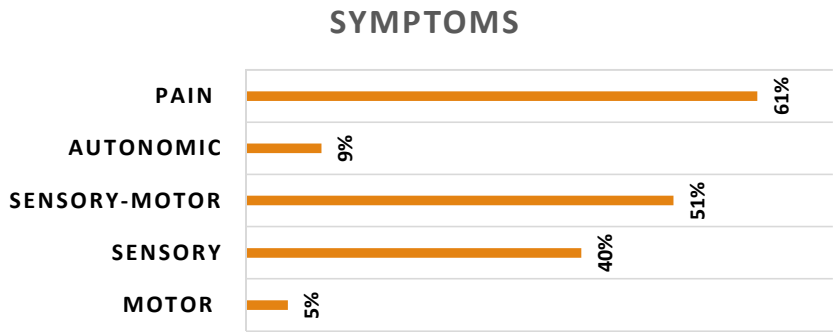
Results

- **Total number of charts reviewed: 100**
- **Demographics:**
  - **Mean Age : 57.91 ± 14.95**
  - **Gender: Male 57, Female 43**
- **Positive family history: 25**

Results

Symptoms	# of patients
Pain	61
Autonomic	9
Sensory	40
Motor	5
Sensorimotor	51
Balance problems	57

Signs	#of patients (n=100)
Sensory only	22
Motor only	3
Sensorimotor	60
Signs	**#of patients**
Foot drop	17
Foot deformities	42



EDX	Axonal	Demyelinating
Sensory only	6	3
Motor only	5	2
Sensorimotor	41	12

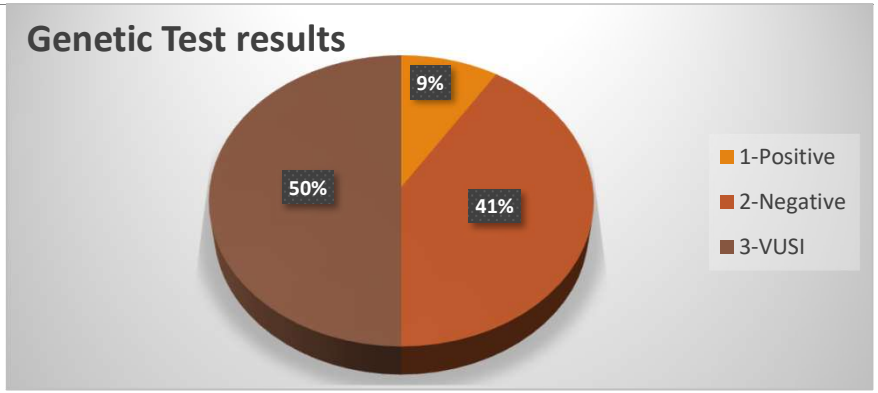
No large fiber neuropathy : 31 patients

Results: Genetic testing

Positive: 9

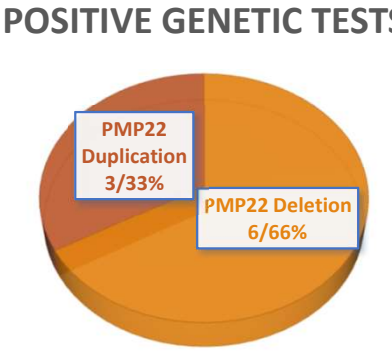
Negative: 41

Variants of unknown significance: 50



Positive:

- **PMP 22 duplication: 3**
- **PMP 22 deletion: 6**



Results/VUS

Total number of mutations seen :42 mutations

More than one mutation seen in :27(64%)

One mutation: 15(36%)

Most common mutations seen: PRX(5/12%)

Variant Gene	Number of patients	Heterozygous	Dominant vs recessive	Other Associated gene (no patients)
MED25	2	yes	AR	no
AARS	3	yes	AR	LMNA
TRPV4	3	yes	AD	CHCHD10 ;SCN10A, WNK1
IGHMBP2	2	yes	AR	no
ALMS1	1	yes	AR	no
COL6A1	1	yes	AR	no
VRK1	1	yes	AR	no
SYNE2	1	yes	AR	no
KIF1A	2	yes	AR	no
MATR3	1	yes	AD	SELENON
GARS	2	yes	AD	no
FLNC	1	yes	AD	VCL
REEP1	1	yes	AR	no
DCTN1	2	yes	AD	FB038, SPG11; SETX
CPT1C	2	yes	AR	no
SPTLC1	1	yes	AD	no
LMNA	1	yes	AR	AARS
PRX	5	yes	AR	SETX ; SCN11A; WNK1
DYNC1H1	2	yes	AD	SLC52A2; SCN11A
SCN10A	3	yes	AD	IKBKAP, SPTLCZ ; TRPV4, WNK1

Type of inheritance:

AD 25(59.5%)

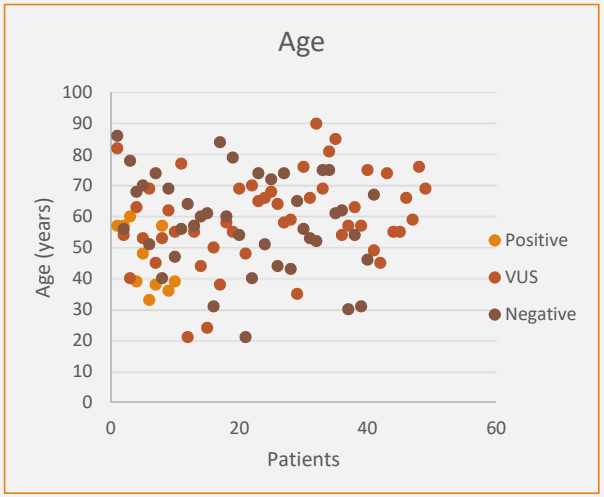
AR 15(35.7%)

X-linked: 2(4.8%)

Variant Genea	Number of patients	Heterozygous	Dominant vs recessive	Other Associated gene (no patients)
DST	2	yes	AR	EGR2, SETX; FBX038
AIFM1	1	yes	X-link	ATP,7A, GJB1, LAS1L, PDK3, PRPS1, UBA1
PLEKHG5	1	yes	AR	no
FBX028	2	yes	AD	DST
IKBKAP	2	yes	AR	SCN10A, SPTLCZ
SBF2	1	yes	AD	no
GJV1	1	yes	X-link	LRSAM1
SCN11A	1	yes	AD	SCN9A
TXNRD2	1	yes	AR	no
SETX	4	yes	AR	DST, EGR2; PRX; DCTN1
CHCHD10	1	yes	AD	TRPV4
CLCN1	1	yes	AD	FLNC
INF2	1	yes	AR	no
ATL1	1	yes	AD	SH3TC2
SLC52A2	1	yes	AR	DYNC1H1
SH3TC2	1	yes	AR	ATL1
LRSAM1	1	yes	AD	GJV1
SPTLCZ	1	yes	AD	IKBKAP, SCN10A
EGR2	1	yes	AR	DST, SETX
SPG11	1	yes	AR	DCTN1, FB038
VCL	1	yes	AD/AR	FLNC
SELENON	1	yes		MATR3

Results

	Positive (n=9)	VUS (n=50)	Negative(n=41)
Age	49±13.6	65±14.3	58.6±18.1
Gender			
Male	5 (56%)	27(54%)	25(61%)
Female	4(44%)	23(46%)	16(39%)
Family history	6(66%)	9(18%)	10(24%)



Results

	Positive (n=9)	VUS (n=50)	Negative (n=41)
Pain	8(88%)	32(64%)	22 (54%)
Sensory	9 (100%)	45(90%)	37(90%)
Motor weakness	8(88%)	35(70%)	21(51%)
Foot deformities	6(66%)	14(28%)	22(54%)
Foot drop	3(33%)	8(16%)	6(14.6%)
CK elevation	3/7(43%)	14/32(44%)	9/20(45%)
EDX testing			
Demyelinating	3(33%)	7(14%)	6(15%)
Axonal	6(66%)	25(50%)	21(51%)
Normal	0	16(32%)	14(34%)

DISCUSSION

1) PMP22 Deletions comprise 80% of the patients with hereditary neuropathy with pressure palsies and PMP22 Duplications comprise 70% of the patients with CMT

66% of our patients with positive test had PMP22 deletions and 33% had PMP22 duplications. PMP22 gene mutation is most common in our group of positive patients

2) Unlike prior conception of no pain in hereditary neuropathy, pain reported in 74% patients with HNPP (Beales, 2017) and in CMT frequency ranges between 56 to 96% (Na Young Jeong, 2013)

88% of our patients with positive genetic testing and 64% with VUS reported pain

3) Sensory symptoms are usually mild and usually distal sensory loss is mostly reported in adults, more common in hereditary sensory neuropathies

Sensory symptoms have been reported by most of our patients and all with positive genetic test result

DISCUSSION

4) Foot deformities become more prevalent with age but are variable even among same-age relatives (Dyck and Lambert 1968)

66% of our patients with positive result had foot deformities

5) Since the early 1990s, over 75 genes have been found to be defective in Charcot-Marie-Tooth disease patients

6) PRX gene encodes L- and S-periaxin, proteins of myelinating Schwann cells, and is mutated in Dejerine-Sottas syndrome (MIM 145900) and Charcot-Marie-Tooth disease type 4F

PRX has been the most common identified mutation in our variants of unknown significance and not associated with any particular phenotype

Conclusion

1) Genetic testing has been positive in only 9% of patients, however variants of unknown significance have been present in 50% of our patients

2) Pain is a prominent feature in most of our patients

3) Foot deformities are common in patients with positive genetic testing, less common in our VUS group

4) No specific phenotype could be identified within the VUS group, probably due to the wide variability and small numbers of each gene mutation identified

Questions & Discussion

THANKS!!!!