Neuropathy.
Nerves before and after TTR.

Márcia Waddington Cruz.

CEPARM HUCFF-UFRJ.

CEPARM

Amyloidosis

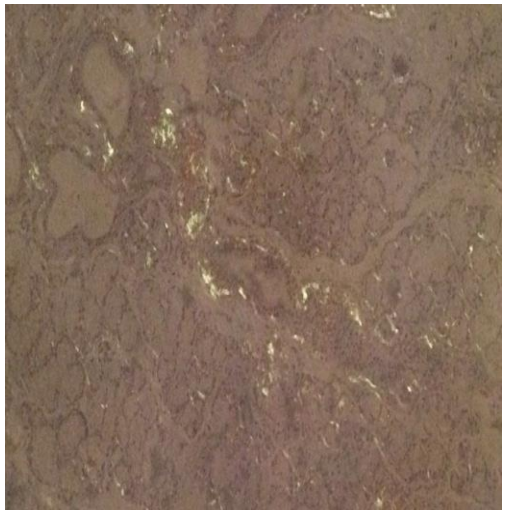
Amyloid deposit.

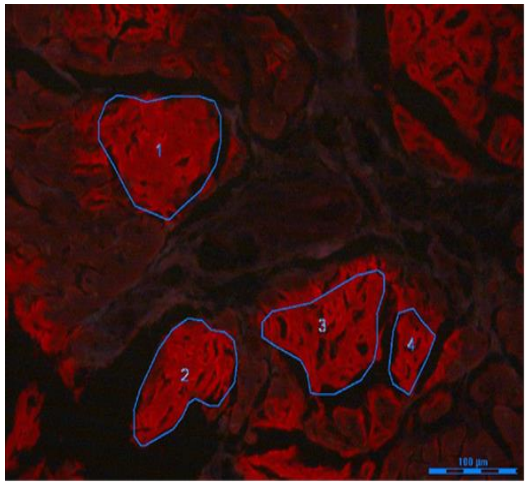
Precursor proteins.

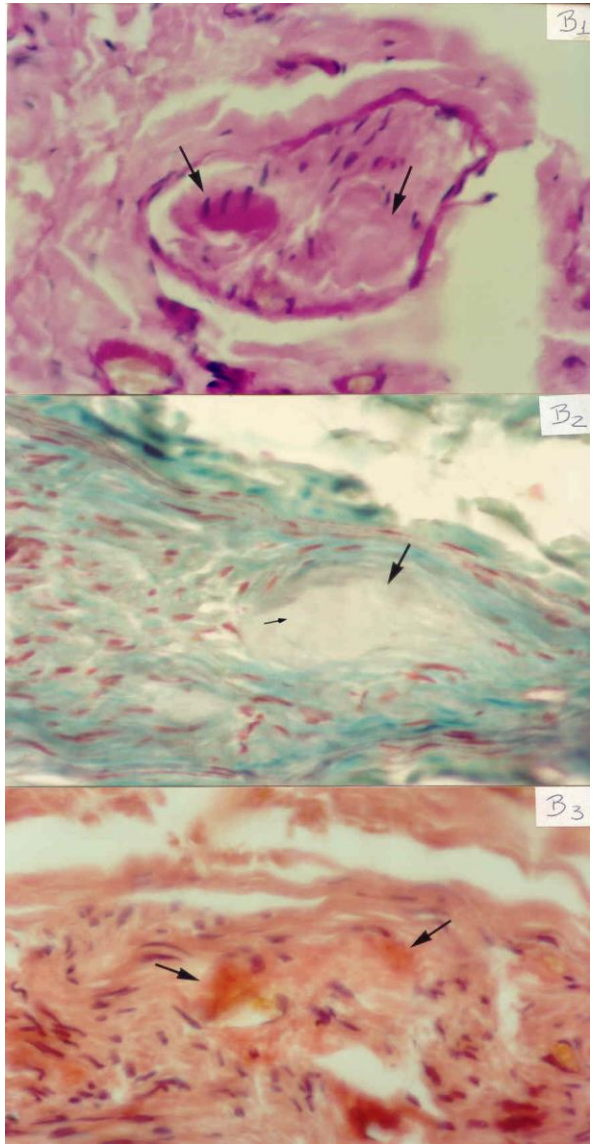
Fibrilar ptn.

Lesion to tissues.

Mechanism?

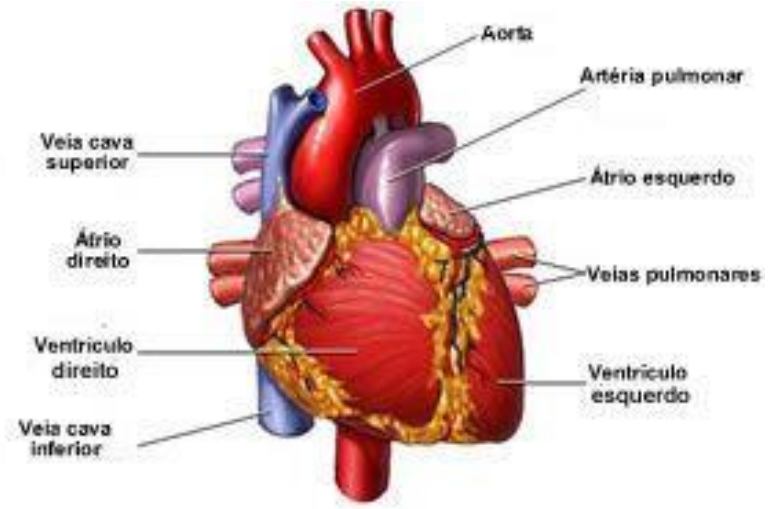




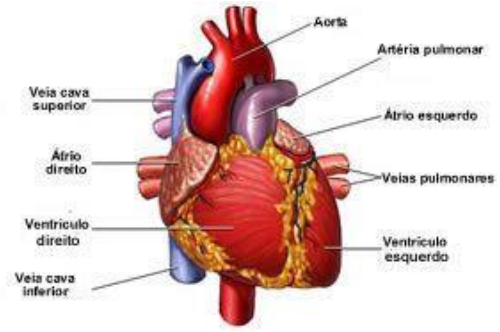


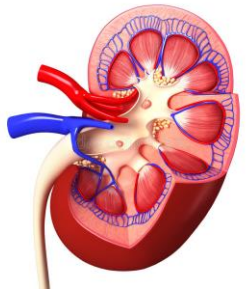
A TTR.

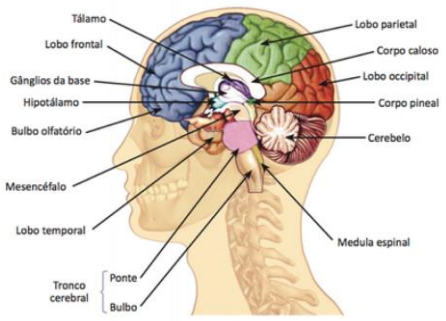
SSA or Wild Type ATTR

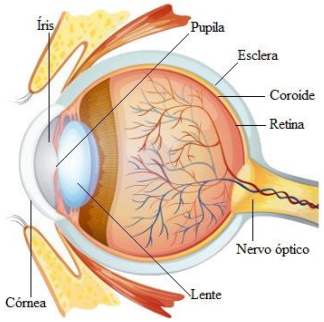


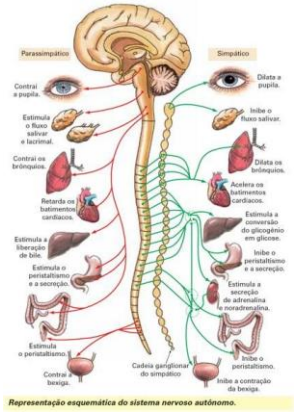
Hereditary ATTR. hATTR.









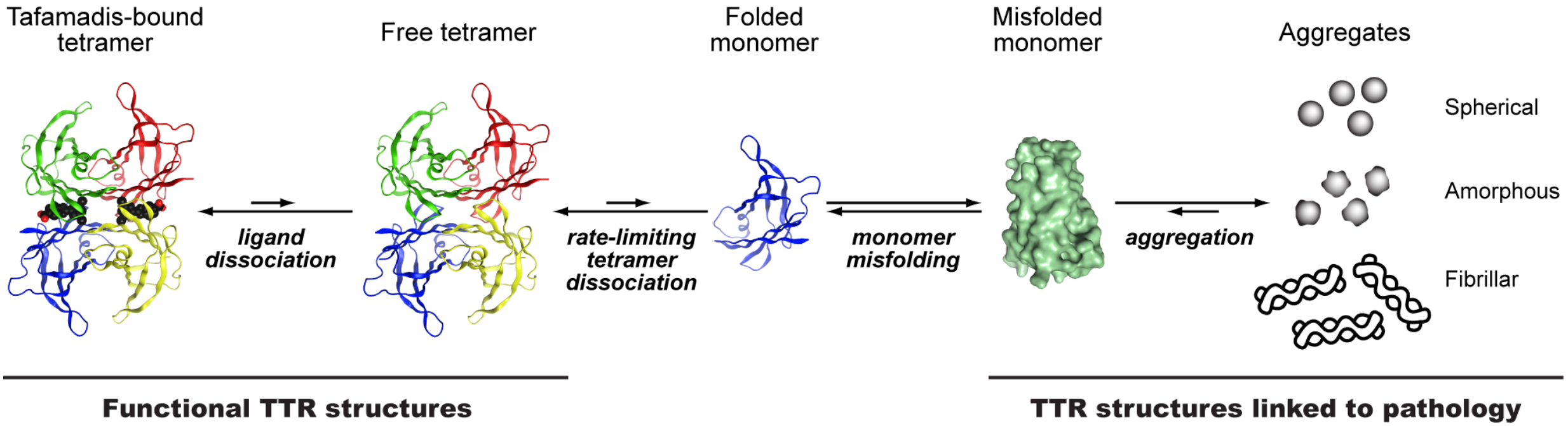


TTR transport vitamin A and tyroxin.

98% production in the liver

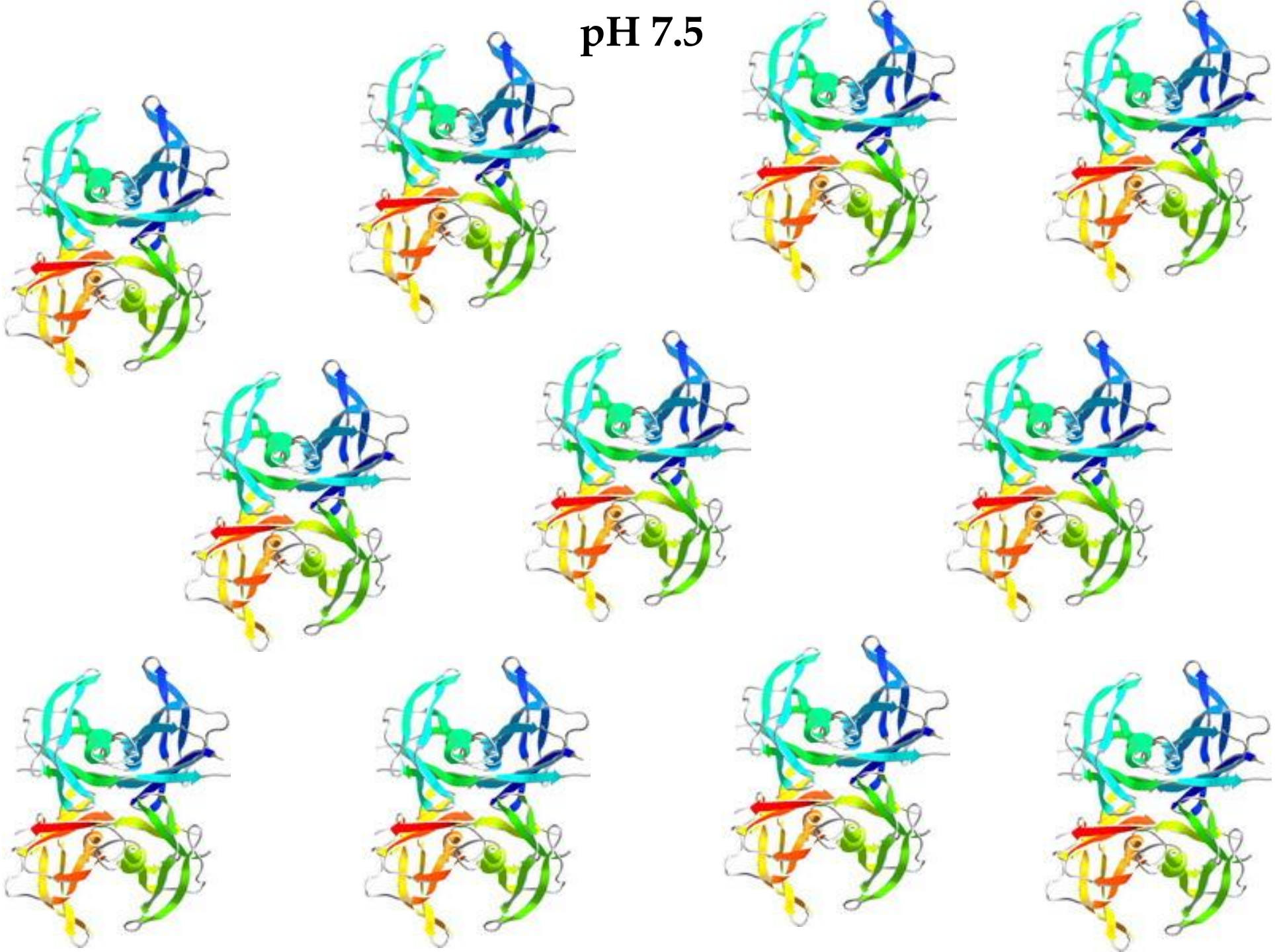
> 100 mutations

V30M most common



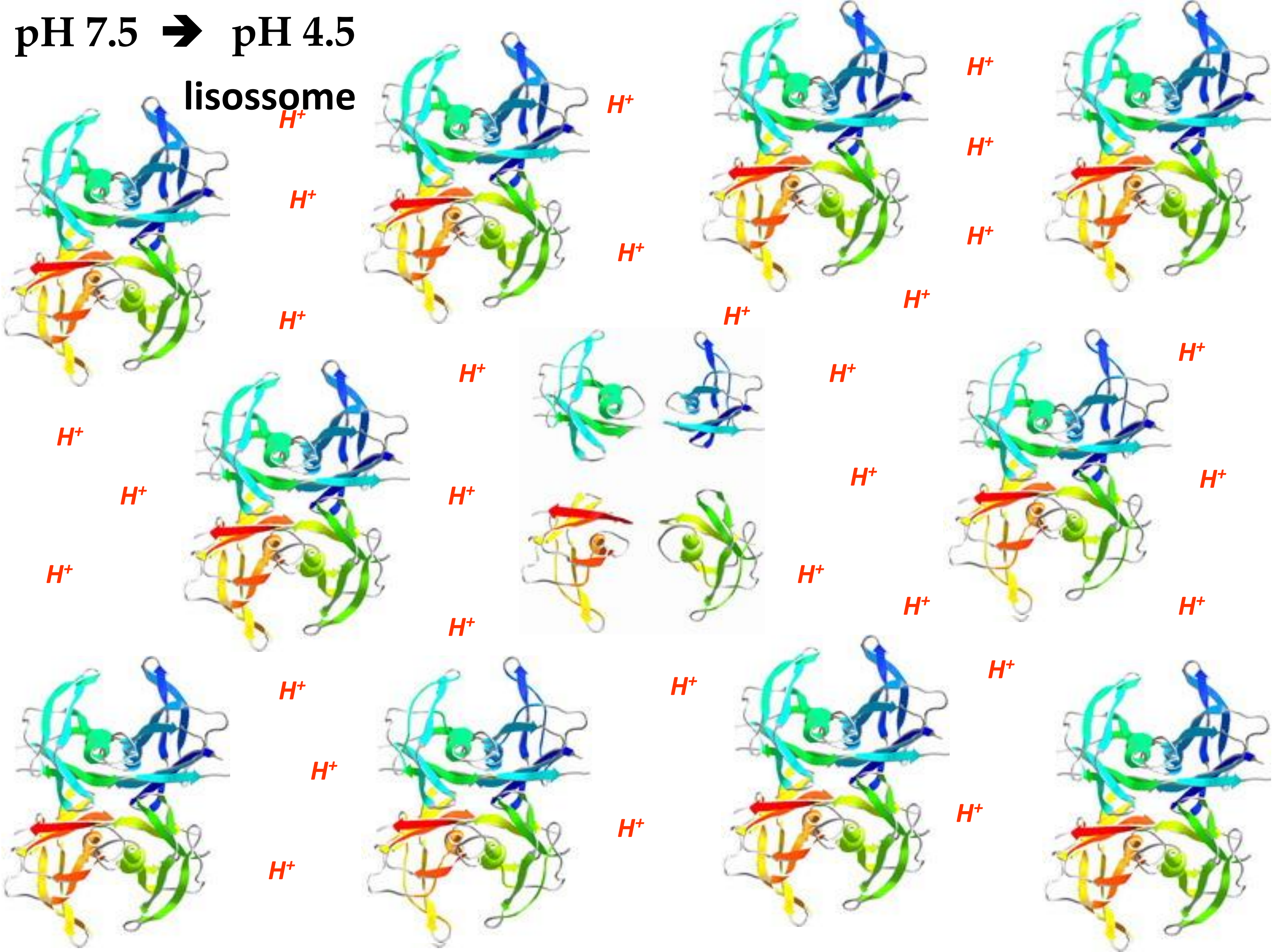
Cortesia do Dr. Jeffrey Kelly.

pH 7.5

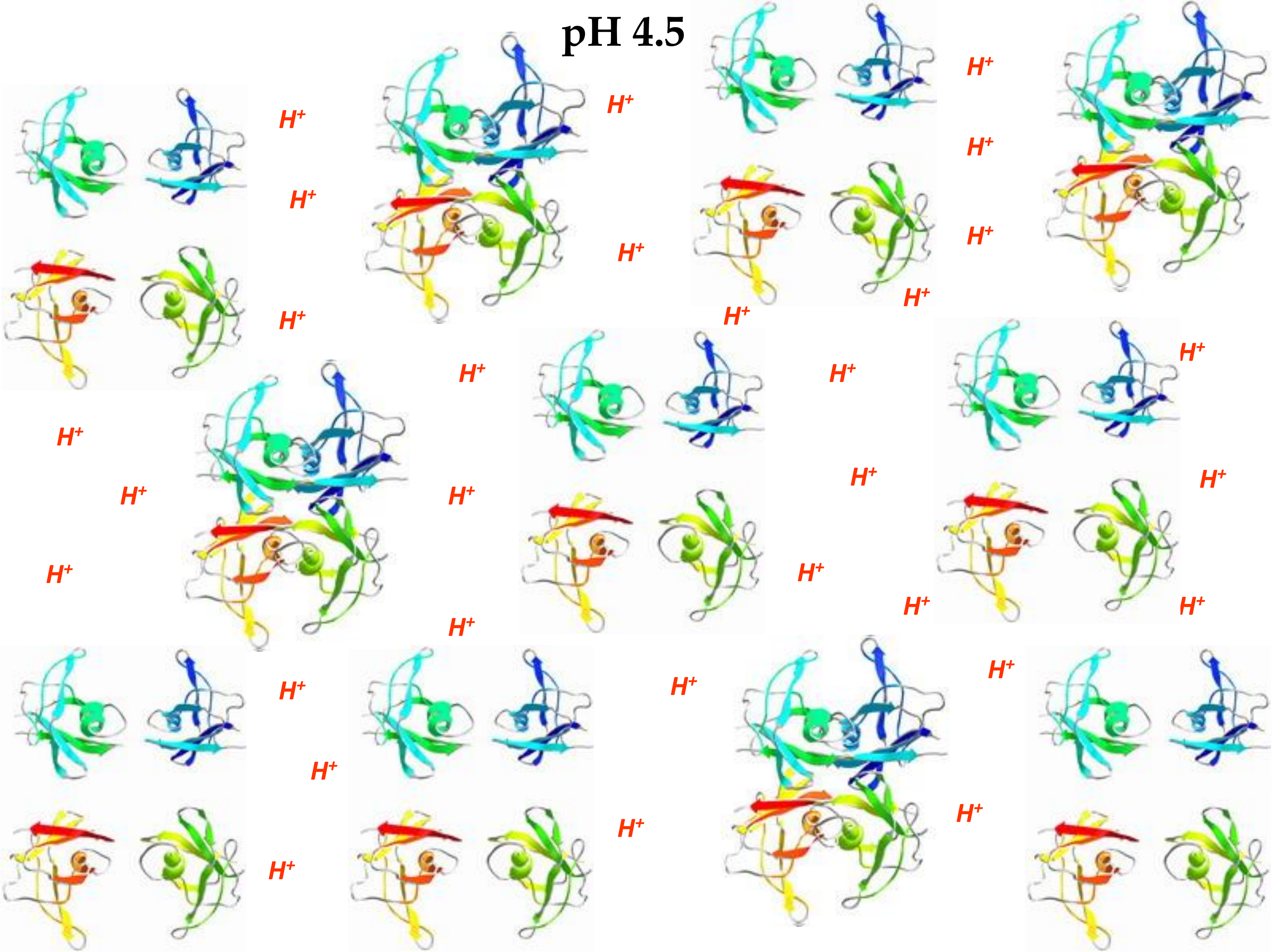


pH 7.5 ➔ pH 4.5

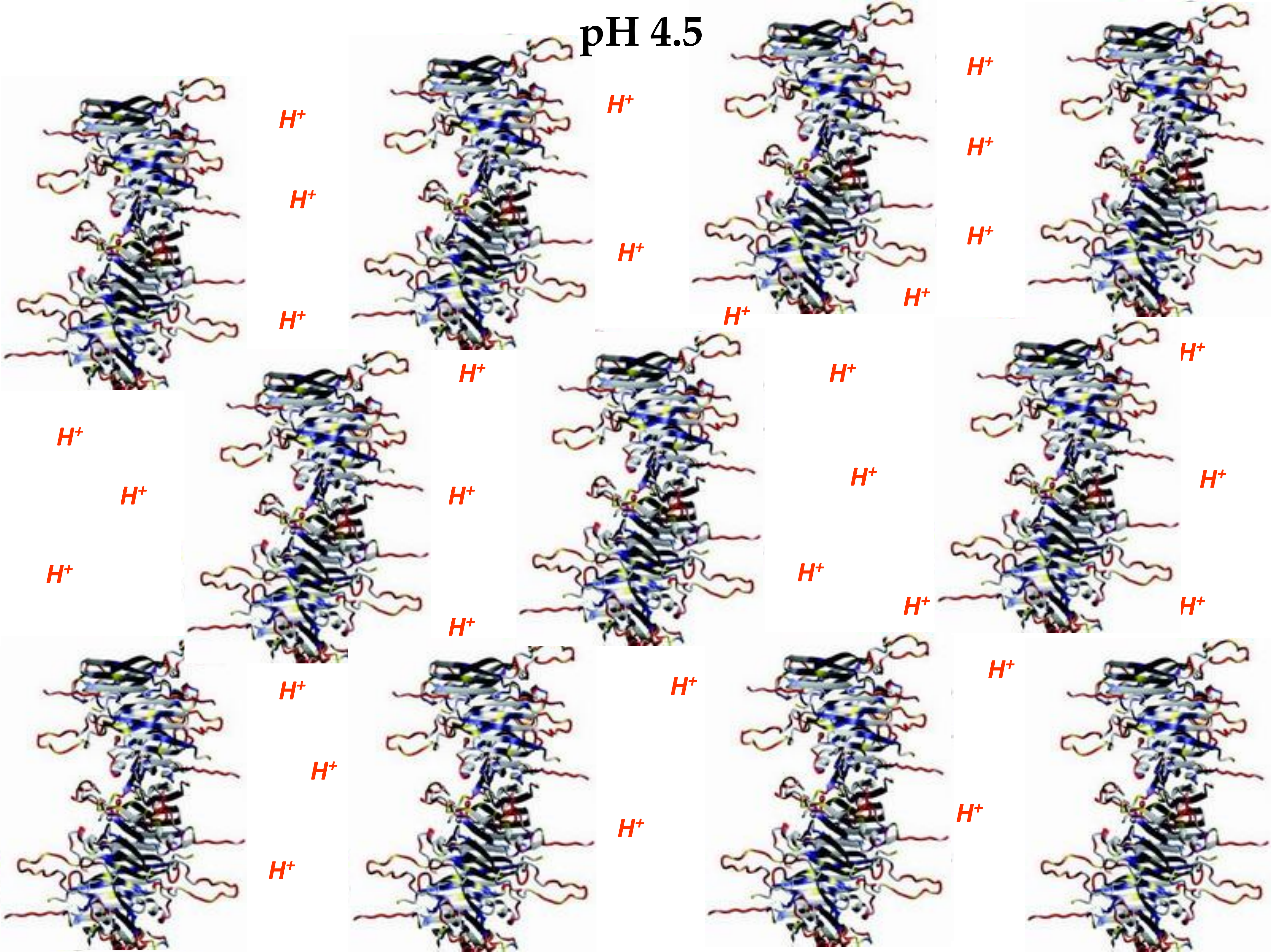
lisossome



pH 4.5

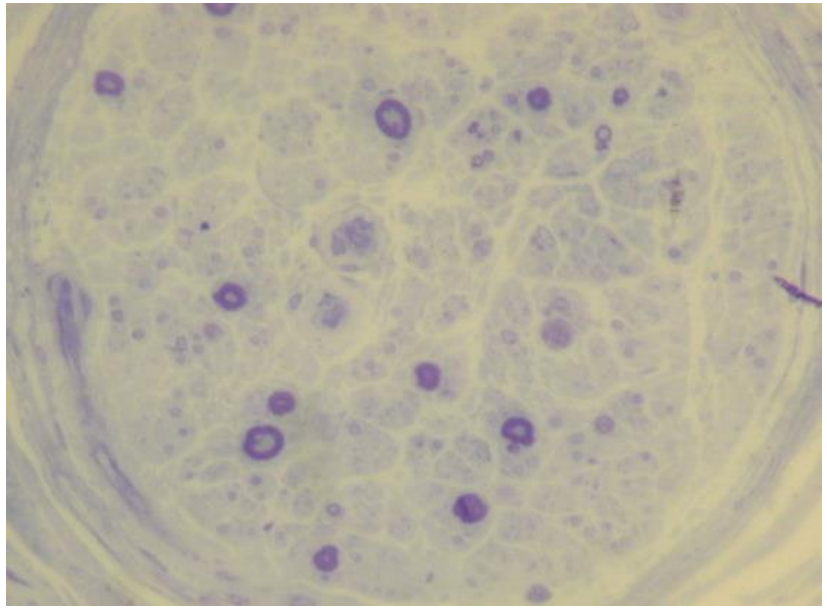


pH 4.5



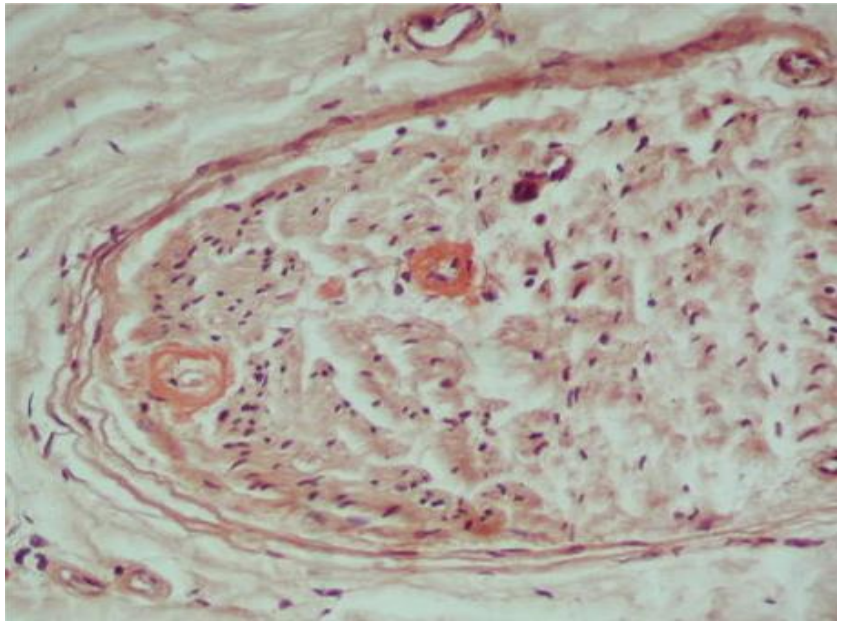
Amyloid endoneurial deposition

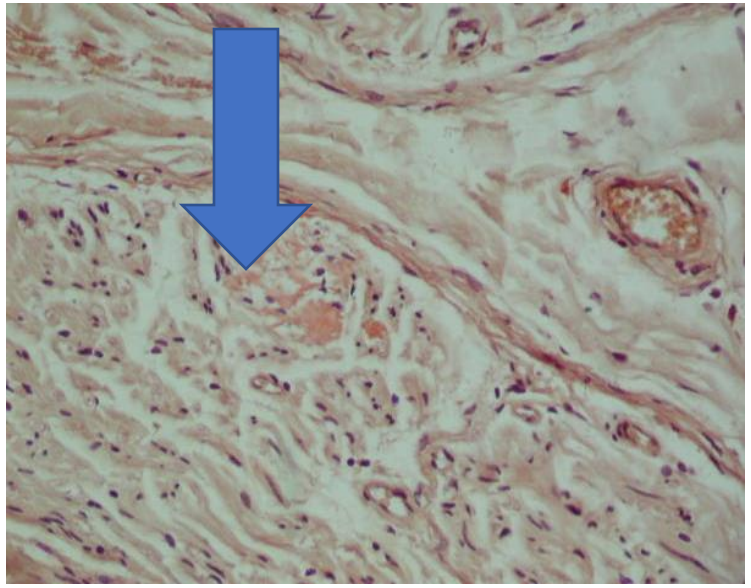
- Axonal loss. Unmylienated fibers
- Small myelinated fibers
- Large myelinated fibers



Early detection of disease. Better treatmemt outcome.

- FAP stage 0 . Congo red - fibers.
- Imunohistochemistry + TTR non fibrilar deposit.
- FAP stage I . Congo red + . Fibrilar amyloid deposit.





HEREDITARY AMYLOIDOSIS

Peptide probes detect misfolded transthyretin oligomers in plasma of hereditary amyloidosis patients

Joseph D. Schonhoft,[1,2]* Cecilia Monteiro,[1,2]* Lars Plate,[1,2] Yvonne S. Eisele,[1,2] John M. Kelly,[2] Daniel Boland,[1] Christopher G. Parker,[1,2,3] Benjamin F. Cravatt,[1,2,3] Sergio Teruya,[4] Stephen Helmke,[4] Mathew Maurer,[4] John Berk,[5] Yoshiki Sekijima,[6] Marta Novais,[7] Teresa Coelho,[7] Evan T. Powers,[1] Jeffery W. Kelly[1,2,3†]

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Increasing evidence supports the hypothesis that soluble misfolded protein asse[illegible]s contribute to the degeneration of postmitotic tissue in amyloid diseases. However, there is a dearth of reliable nonantibody-based probes for selectively detecting oligomeric aggregate structures circulating in plasma or deposited in tissues, making it difficult to scrutinize this hypothesis in patients. Hence, understanding the structure-proteotoxicity relationships driving amyloid diseases remains challenging, hampering the development of early diagnostic and novel treatment strategies. We report peptide-based probes that selectively label misfolded transthyretin (TTR) oligomers circulating in the plasma

Table 1. Sample age and demographics for the non-native TTR detection by the B-2 SDS-PAGE assay presented in Figs. 4G, 6, and 7.

Genotype (*n*)	Female/male	Age (means ± SD)	Origin
Healthy donors (30)	18/12	51 ± 16	United States (28), Japan (2)
V30M asymptomatic (13)	6/7	36 ± 13	Portugal (12), United States (1)
V30M FAP (43)	21/22	43 ± 14	Portugal (34), Japan (7), United States (2)
WT cardiomyopathy (15)	1/14	76 ± 8	United States (15)
V122I (6)	4/2	76 ± 8	United States (6)
Other: T60A (4), F44S (2), T79K (1), T49P (1), I84N (1), S50I (1), and S50R (1)	5/6	56 ± 11	United States (6), Japan (5)

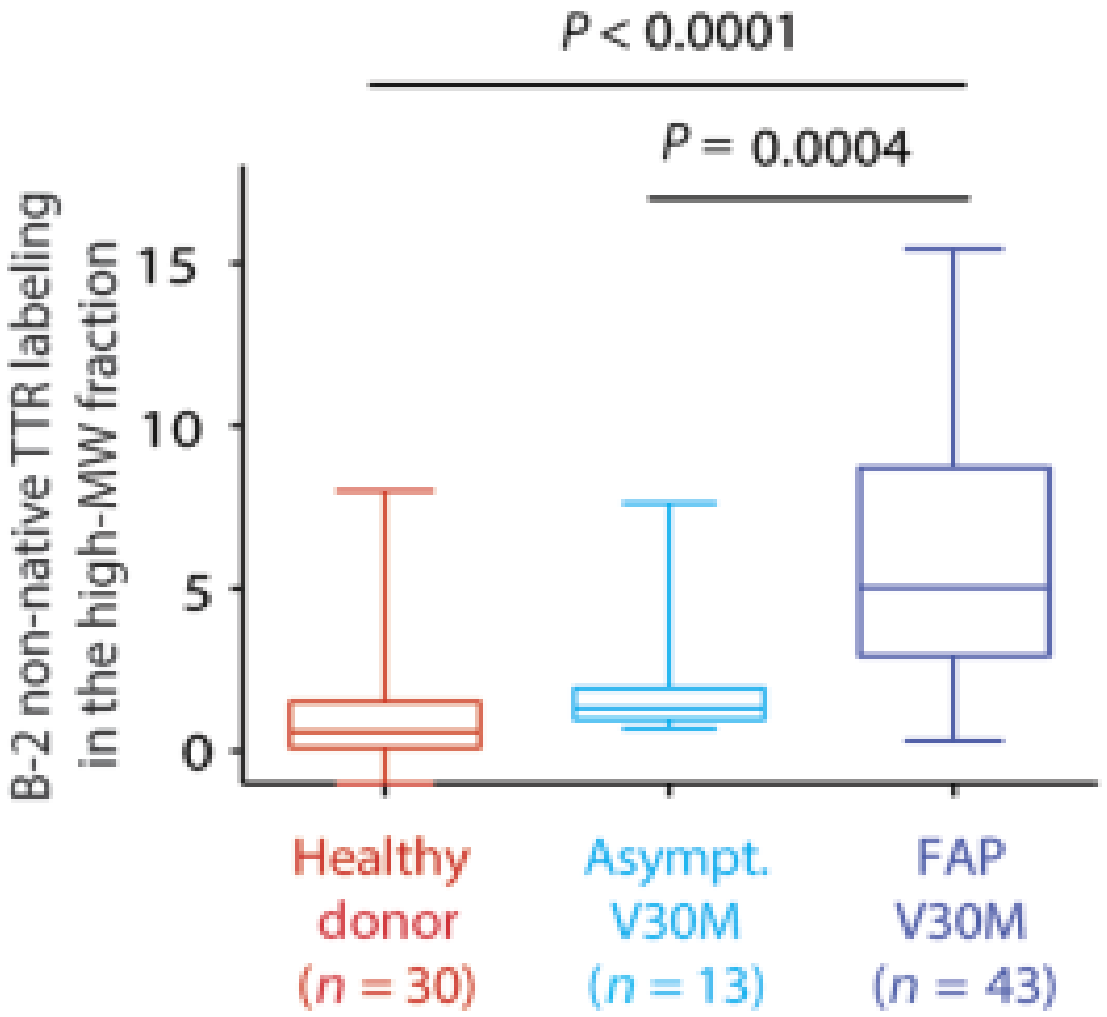


Fig. 3. Probe B-1 selectively differentiates FAP patient samples from controls. (**A**) Experimental setup and representative SEC chromatograms, where

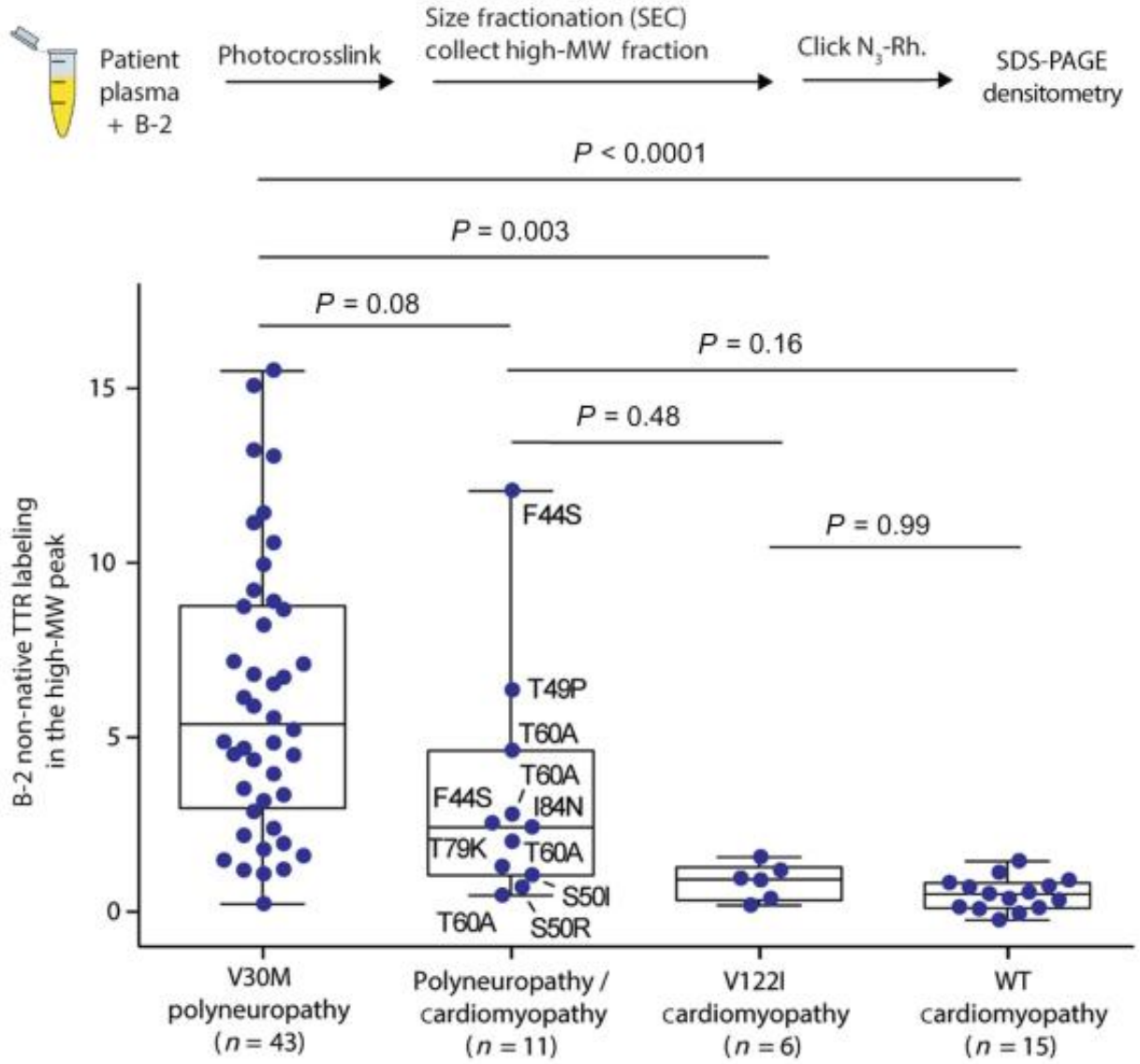


Fig. 7. Non-native TTR is detected in predominantly neuropathic hereditary TTR amyloidosis and not detected in cardiomyopathy-associated genotypes.

[redacted], Misfolded oligomers decrease in TTR amyloid polyneuropathy patients treated with disease-modifying therapies (tafamidis or liver transplant–mediated gene therapy). In a subset of TTR amyloid polyneuropathy patients, the probes also detected a circulating TTR fragment that disappeared after tafamidis treatment. Proteomic analysis of the isolated TTR oligomers revealed a specific patient-associated signature composed of proteins that likely associate with the circulating TTR oligomers. Quantification of plasma oligomer concentrations using peptide probes could become an early diagnostic strategy, a response-to-therapy biomarker, and a useful tool for understanding structure-proteotoxicity relationships in the TTR amyloidoses.

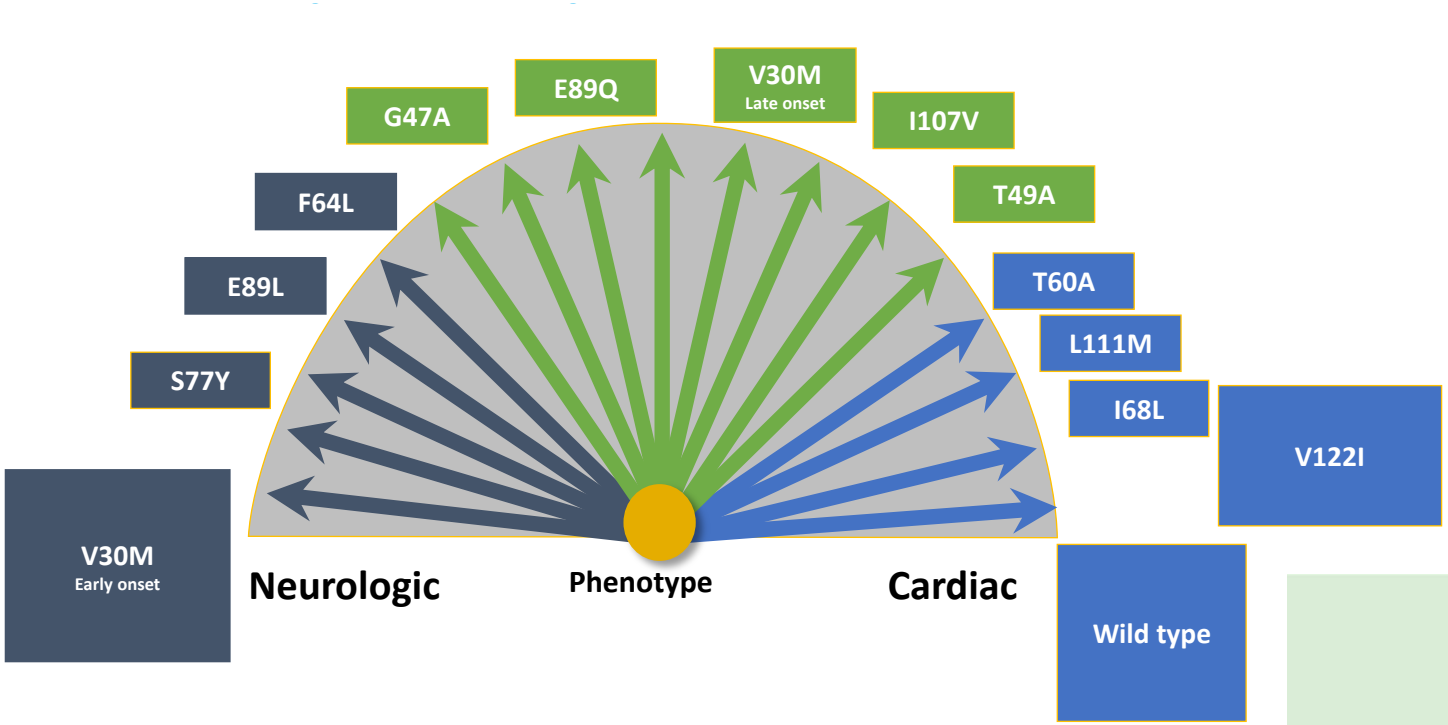
H ATTR. Disease that affects multiple organs

h ATTR PN = FAP and

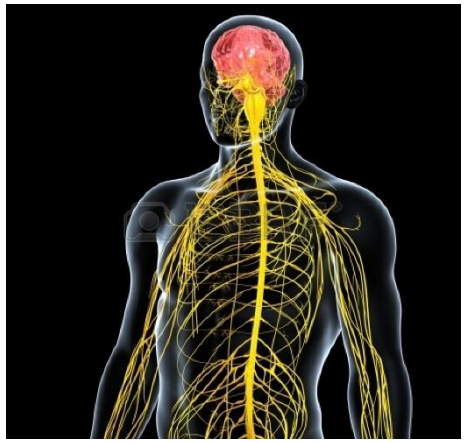
h ATTR CM= FAC

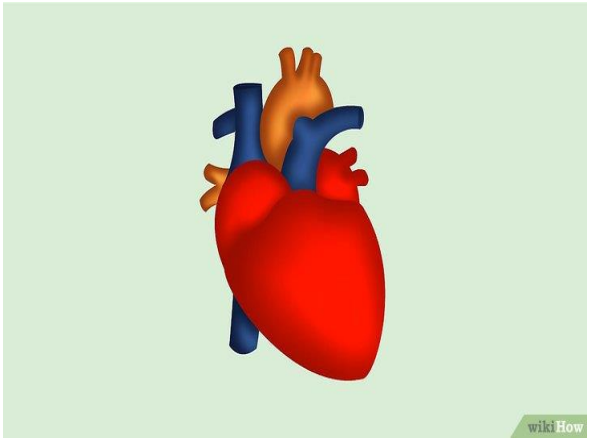
Presentation depends on mutation, age at onset and geo location.

PAF
FAP



CAF
FAC





1. Based on Rapezzi et al. *Eur Heart J* 2013;34:520–8;
2. Coelho et al. *Curr Med Res Opin* 2013;29:63–76

TTR Amyloidosis is a Severe, Progressive Disease Affecting Multiple Organs

Ocular Manifestations

- Vitreous opacities
- Glaucoma
- Abnormal conjunctival vessels
- Papillary abnormalities

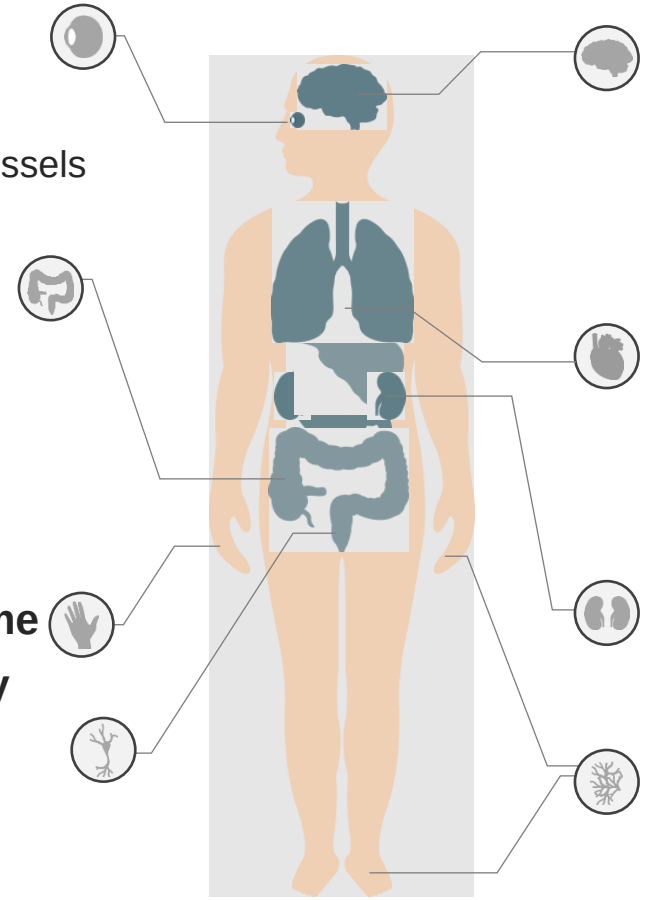
GI Manifestations

- Nausea & vomiting
- Early satiety
- Diarrhea
- Severe constipation
- Alternating episodes of diarrhea & constipation
- Unintentional weight loss

Carpal Tunnel Syndrome

Autonomic Neuropathy

- Orthostatic hypotension
- Recurrent urinary tract infections (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities



Cerebral Amyloid Angiopathy

- Progressive dementia
- Headache
- Ataxia
- Seizure
- Spastic paresis
- Stroke-like episode

Cardiovascular Manifestations

- Conduction blocks
- Cardiomyopathy
- Arrhythmia

Nephropathy

- Proteinuria
- Renal failure

Peripheral sensory-motor neuropathy

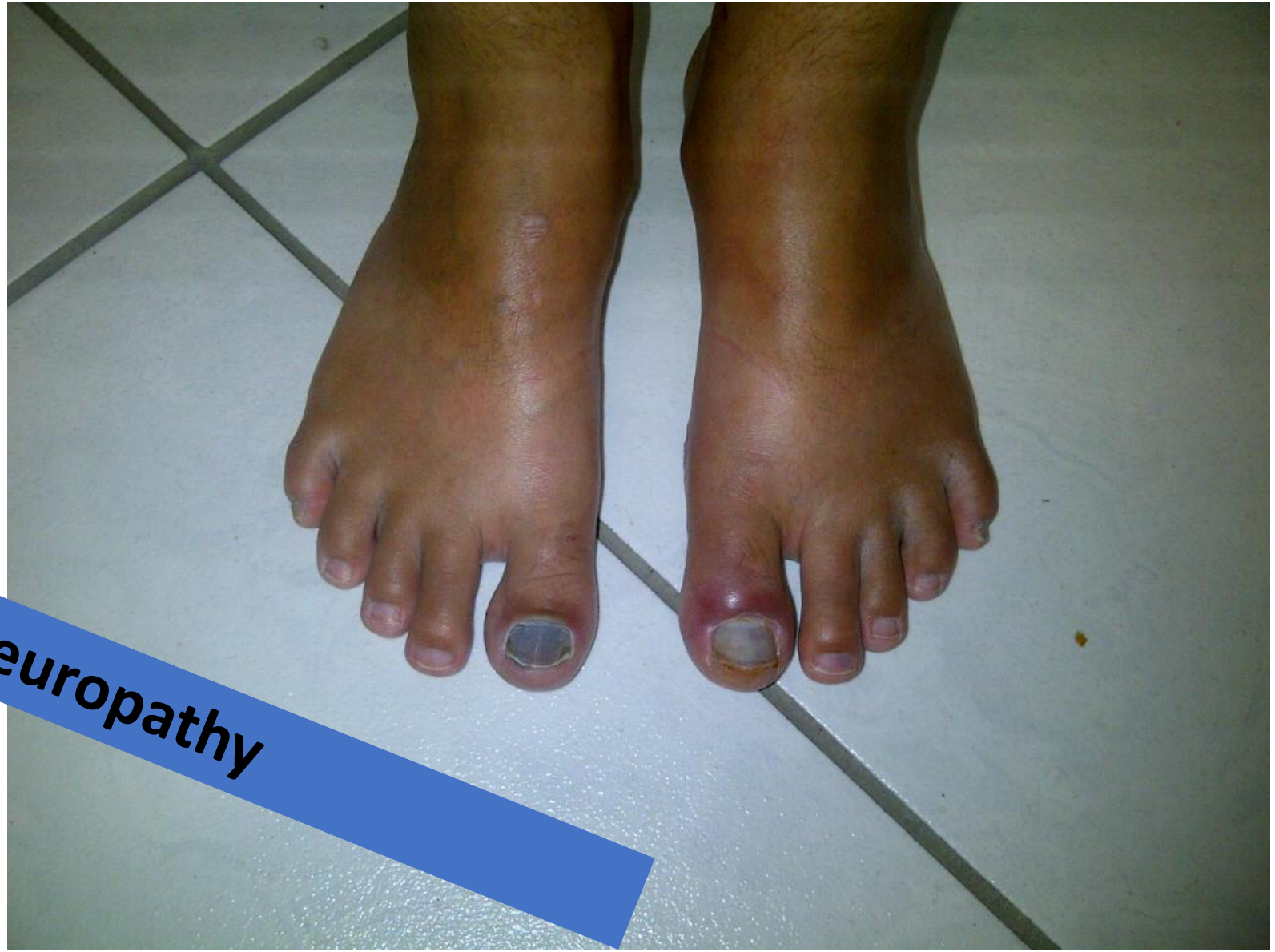
- Typically axonal, fiber-length-dependent, symmetric, and relentlessly progressive in distal to proximal direction

Adapted from: Conceicao et al, First Congress of the European Academy of Neurology (EAN), June 20-23 2015, Berlin, Germany (#P1184)

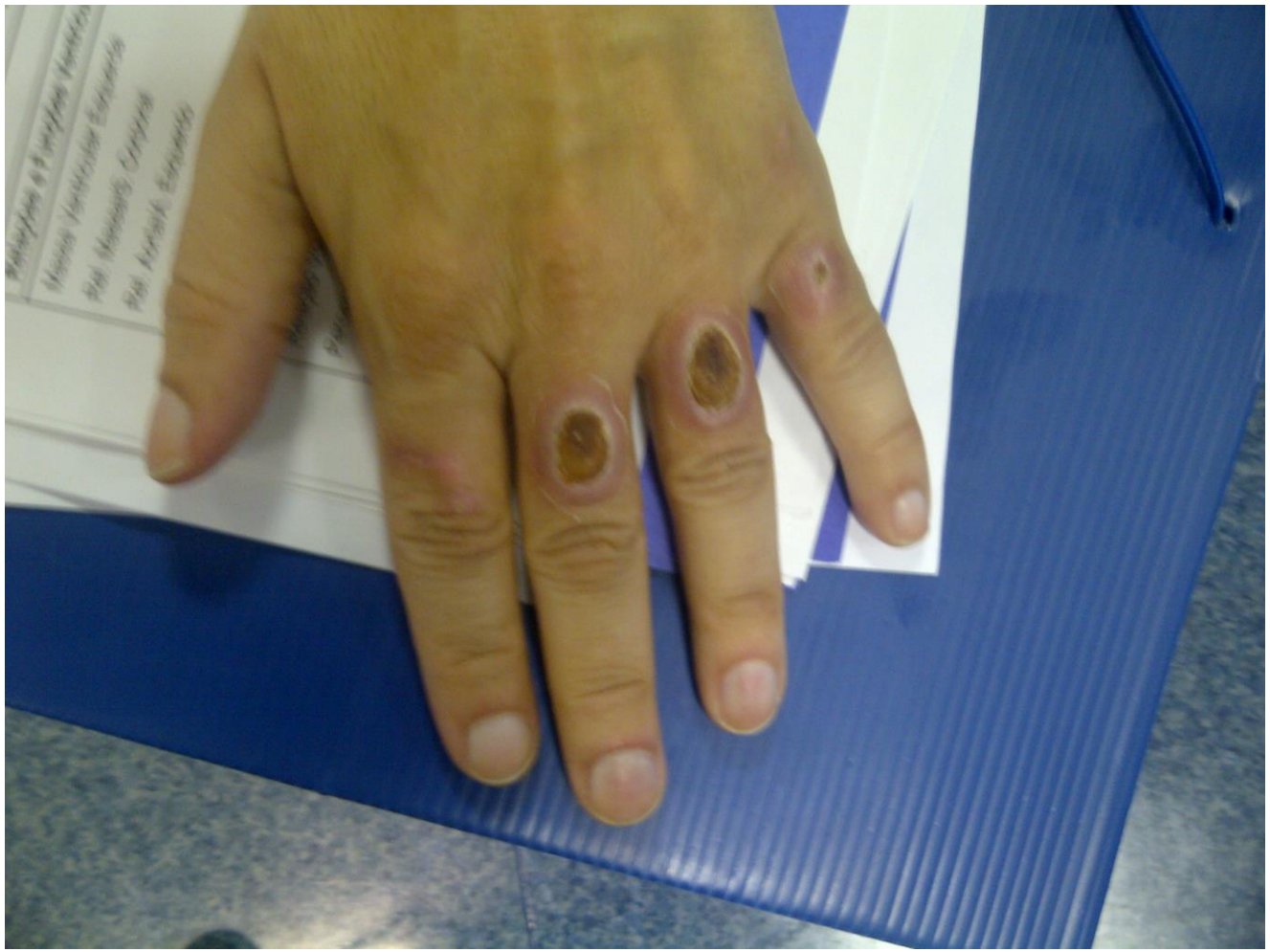
TTR-FAP disease progression

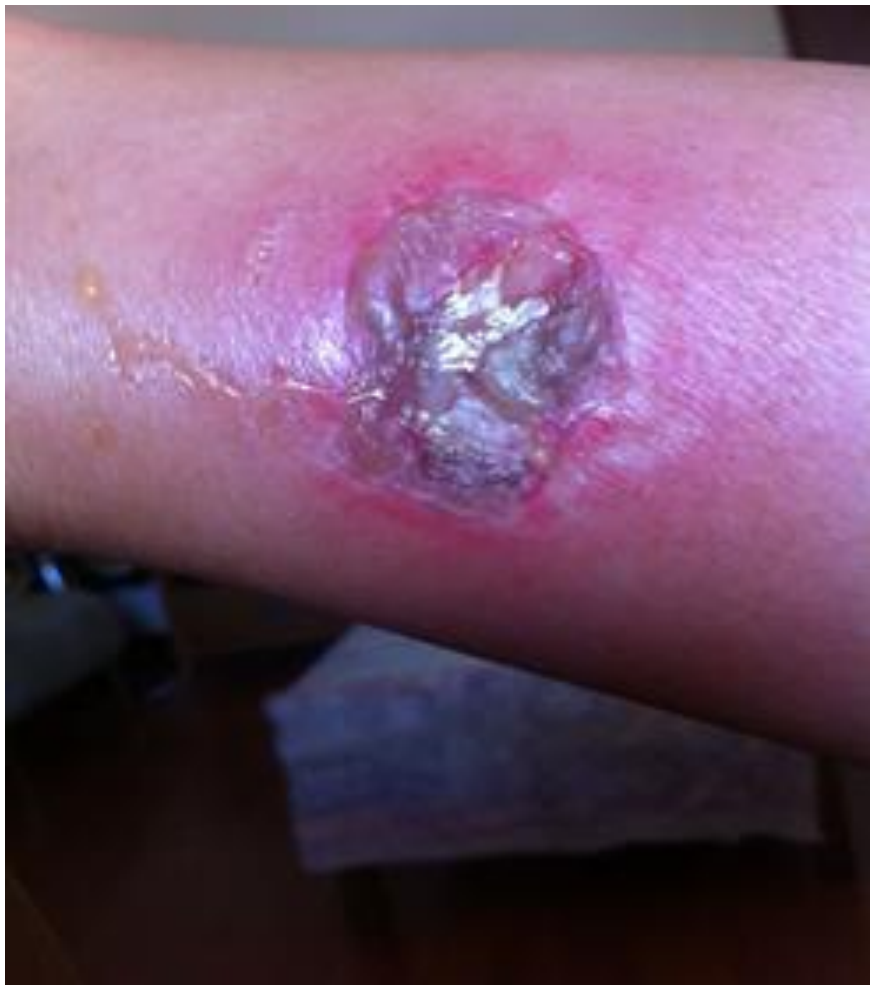
- Patients with TTR-FAP experience a progressive loss of sensory, motor, and autonomic nerve function[2]

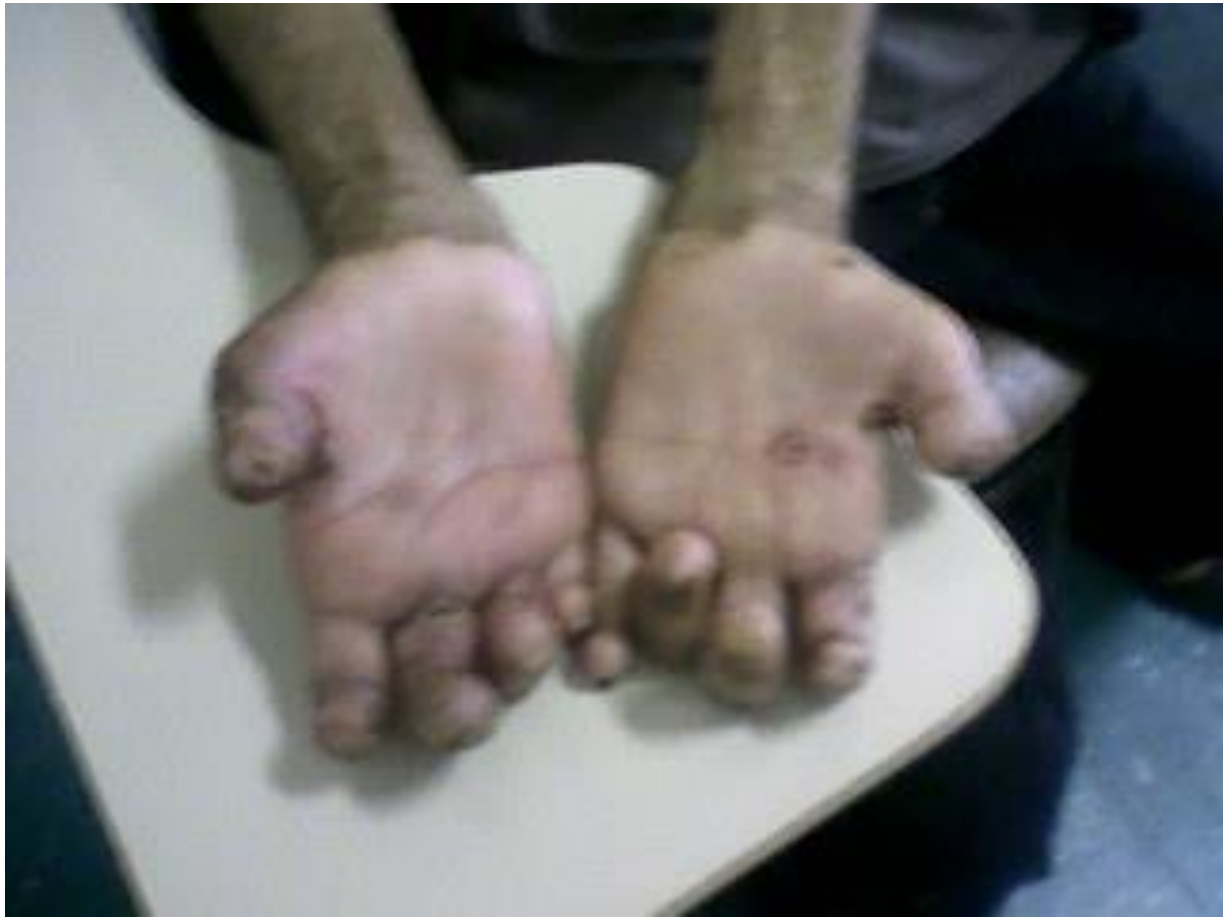
1. Ando Y et al., *Orphanet J Rare Dis.* 2013; doi: 10.1186/1750-1172-8-31; 2. Adams D, et al., *Curr Opin Neurol.* 2016; 29(Suppl 1):S1–S2.

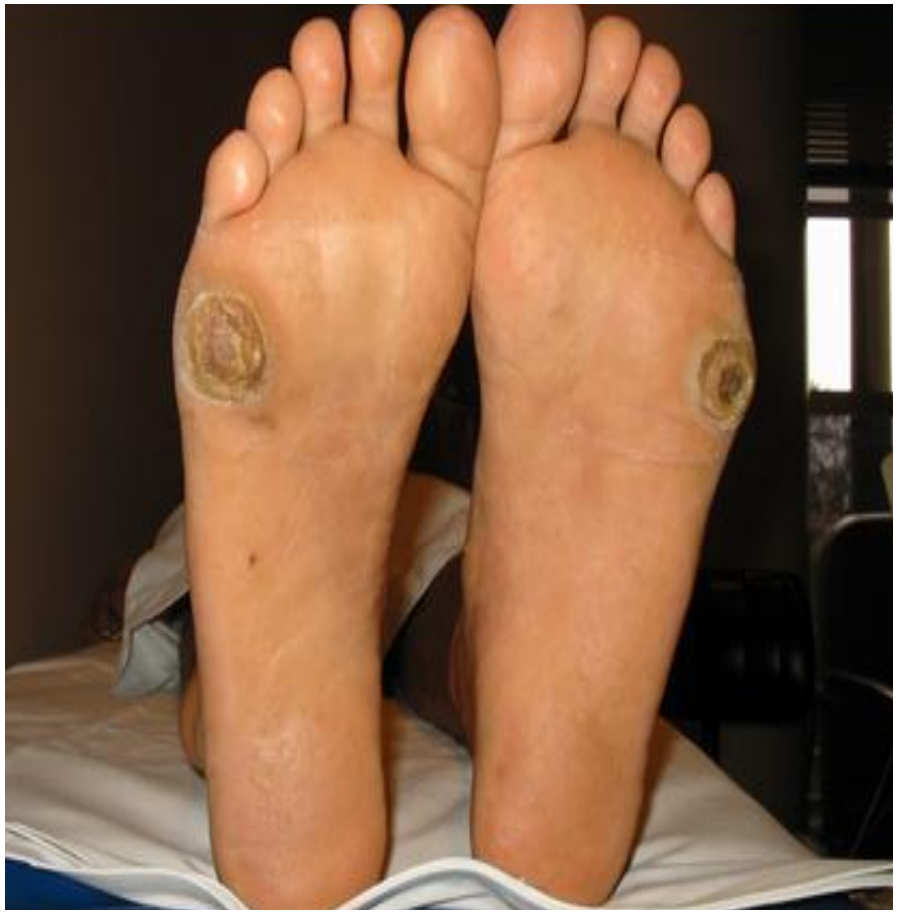


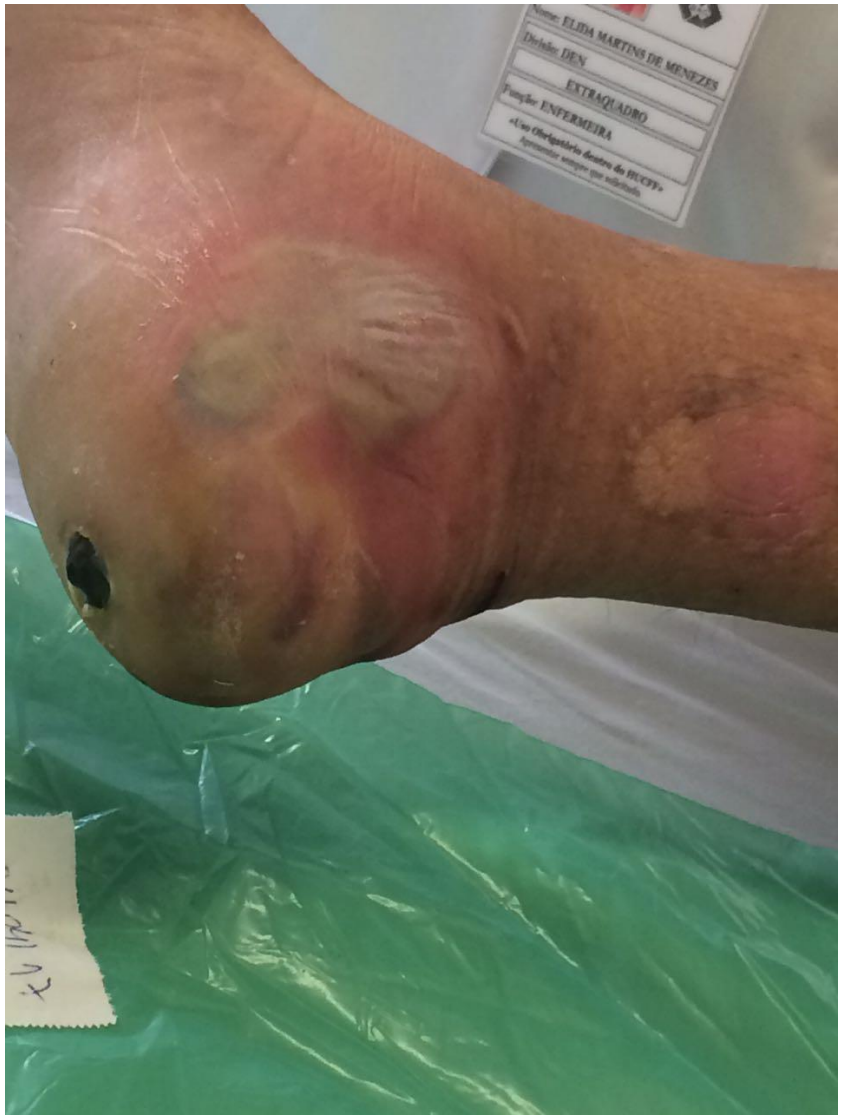
Sensory neuropathy

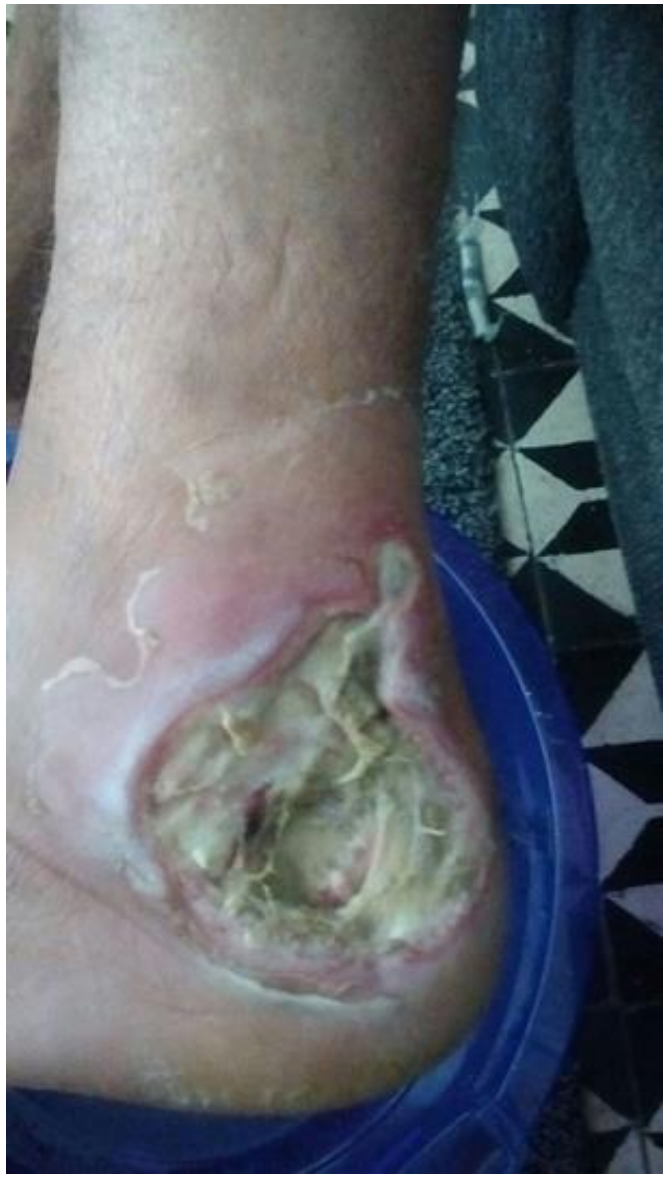




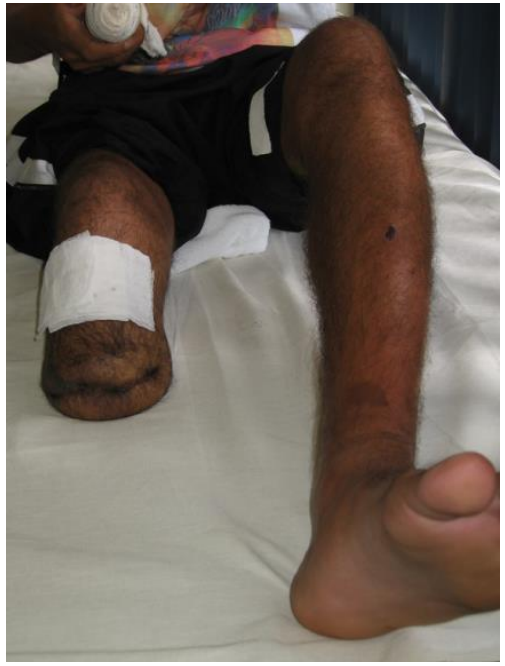





Nome: ELIDA MARTINS DE MENEZES
Distrito: DEN
EXTRAQUADRO
Função: ENFERMEIRA

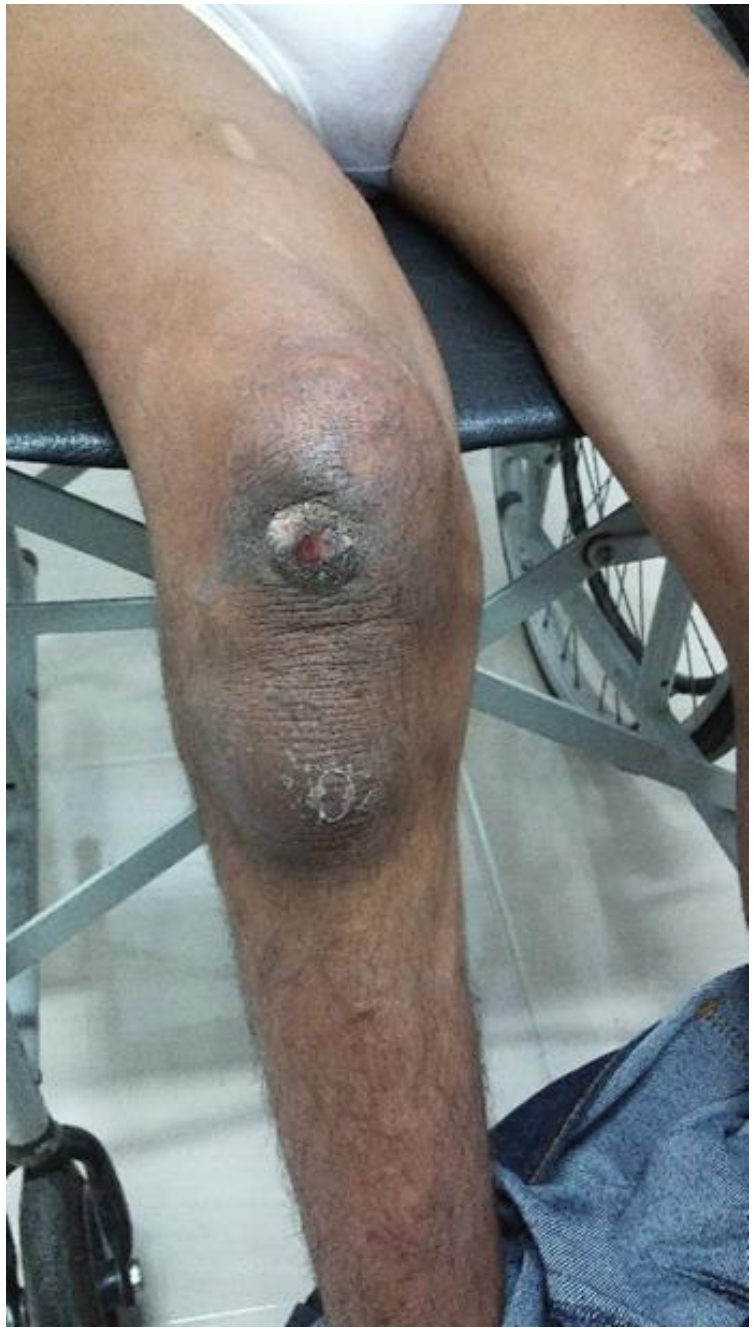


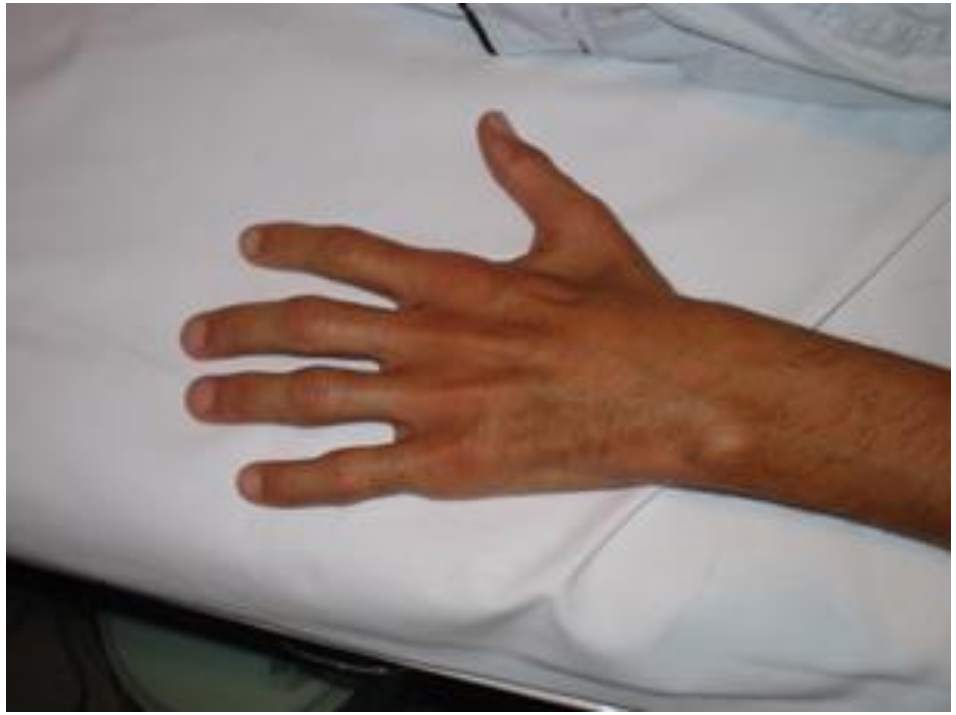
The relentless progression of TTR-FAP

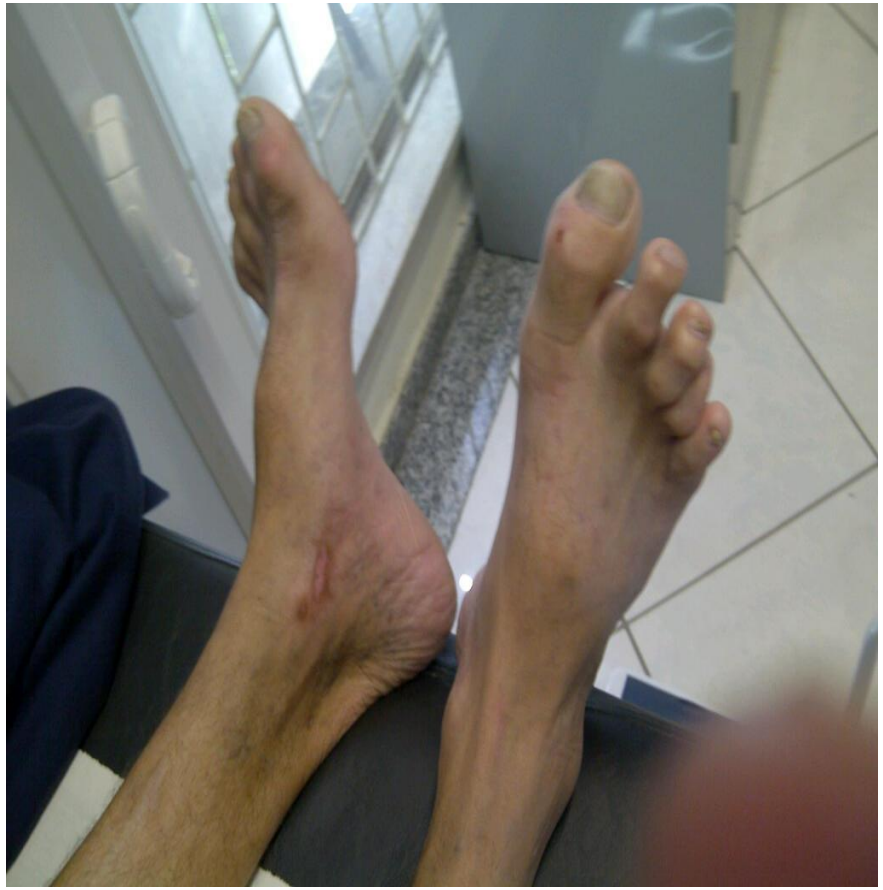


Diagnosis at 2013; Disease since 2011; Family history present; PND I; Bad social background.

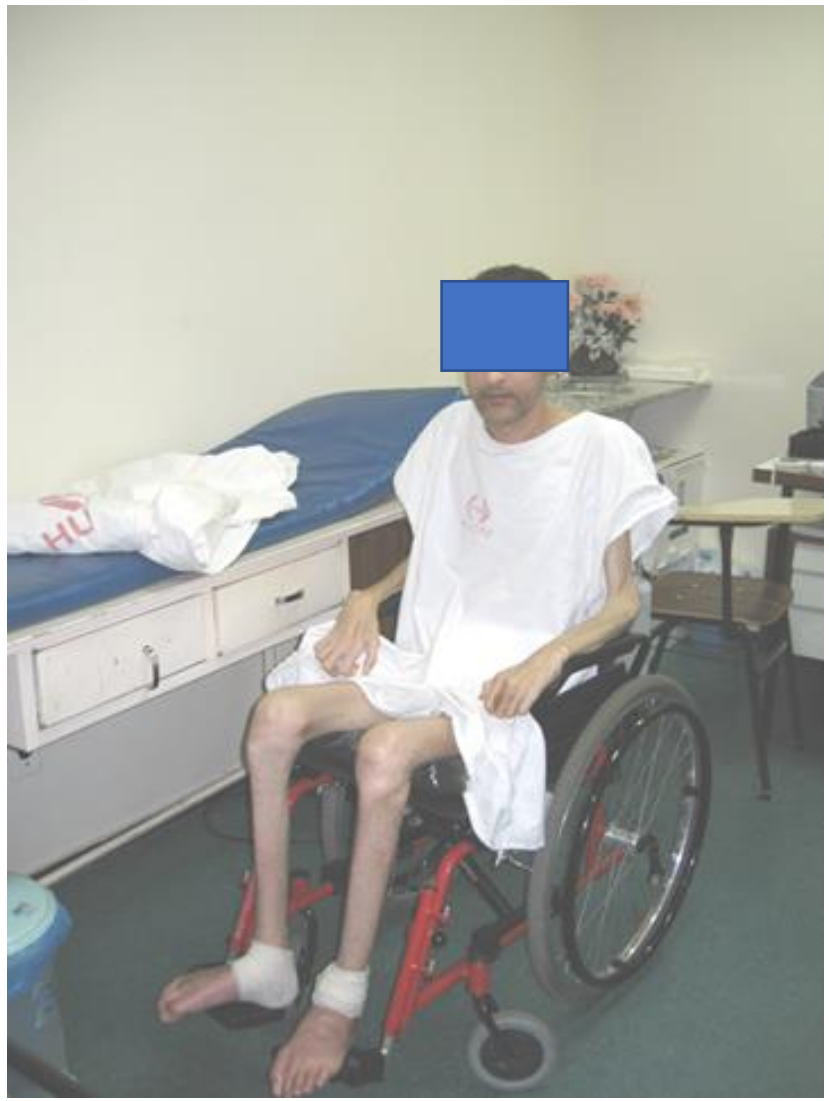
Val30Met; Family history present; Diagnosis in 2013; Disease onset in 2010; PND II.

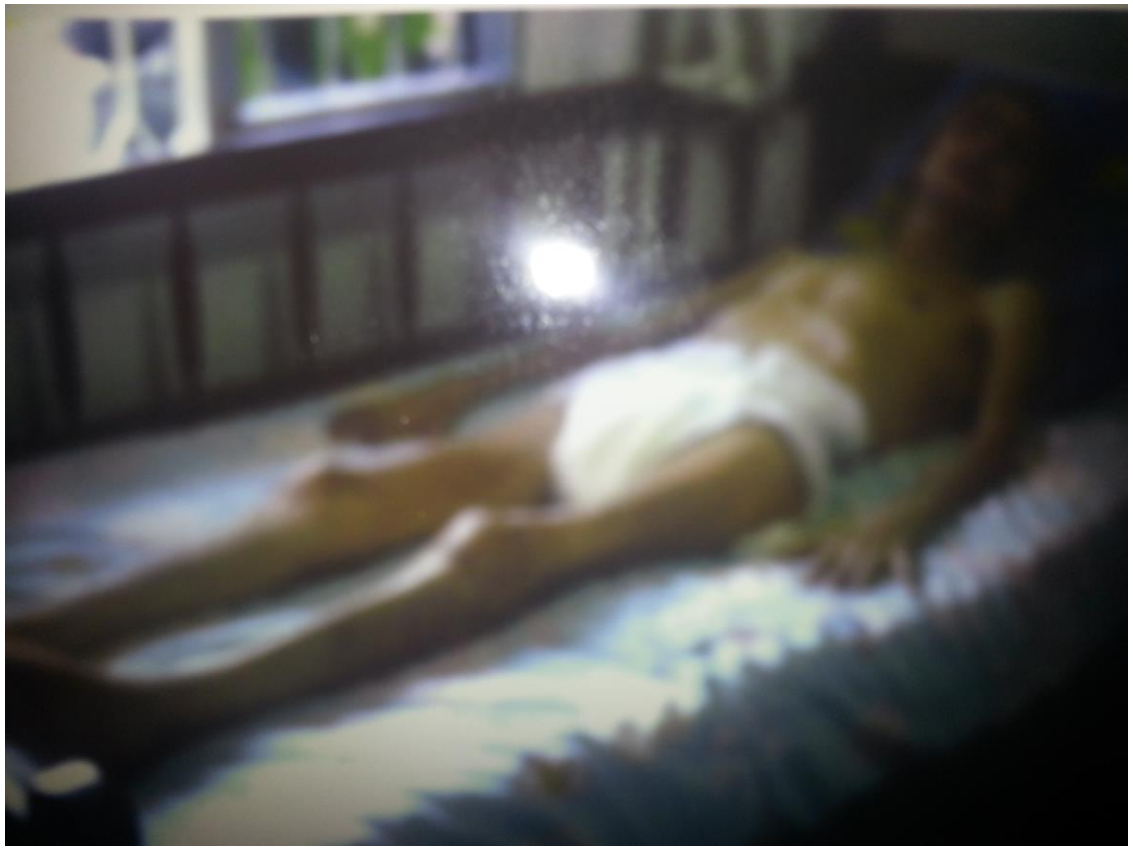




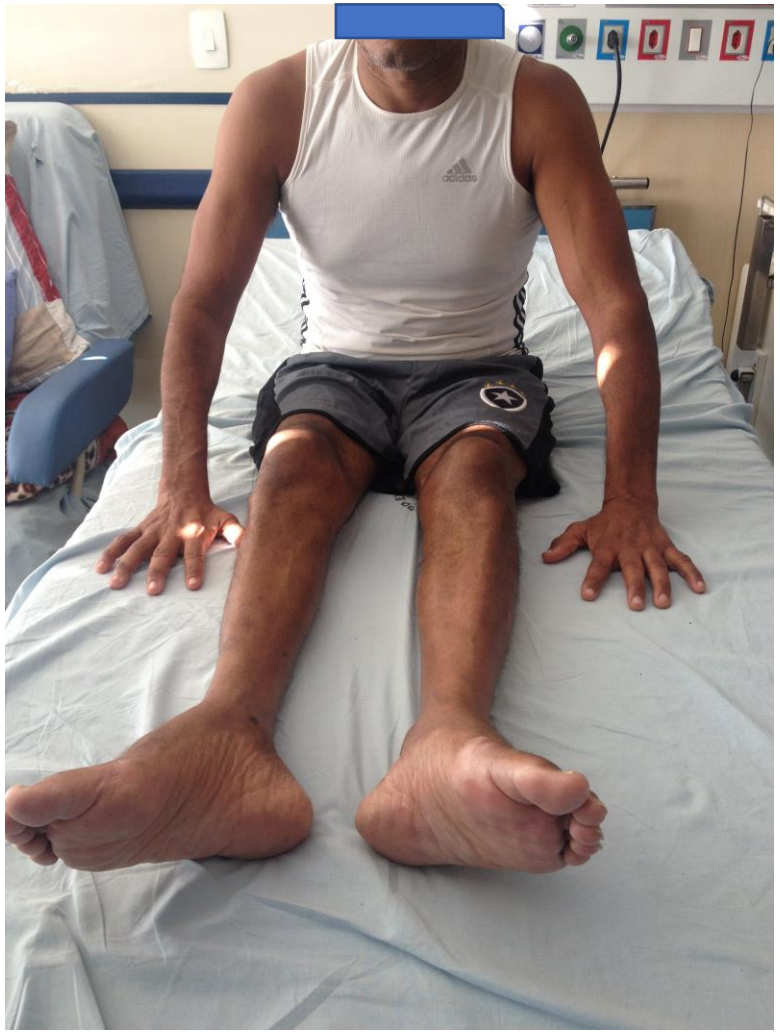


Motor neuropathy

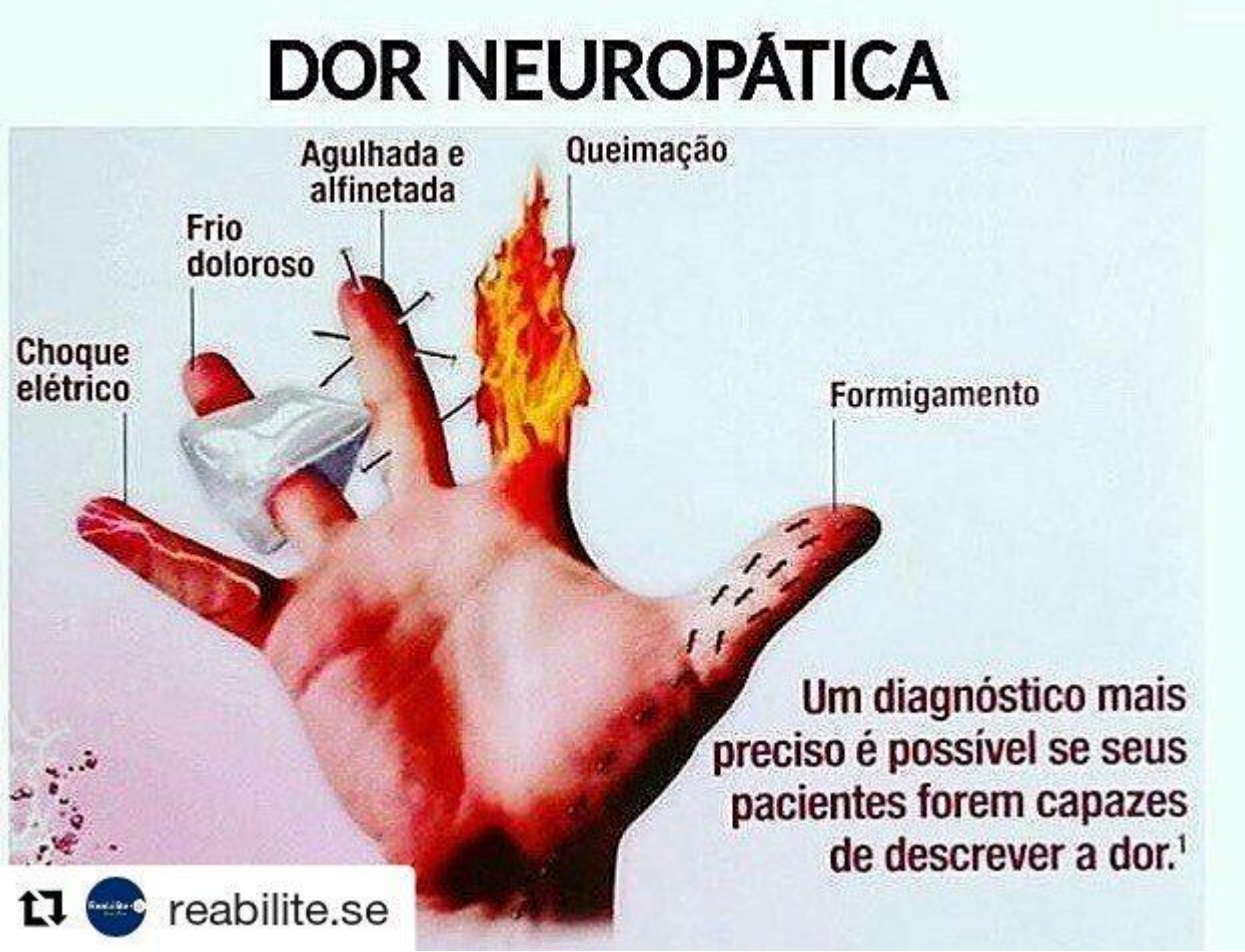





Ano: 1994



Neuropathic pain



Autonomic Neuropathy

- **Vomiting.**
- **Diarrhea / Constipation**
- **Urinary tract infections.**
- **Bladder/ Bowel incontinence.**
- **Sexual disfunction**
- **Orthostatic Hypotension**
- **Massive loss of body weight.**

Autonomic Neuropathy. GI abnormalities.

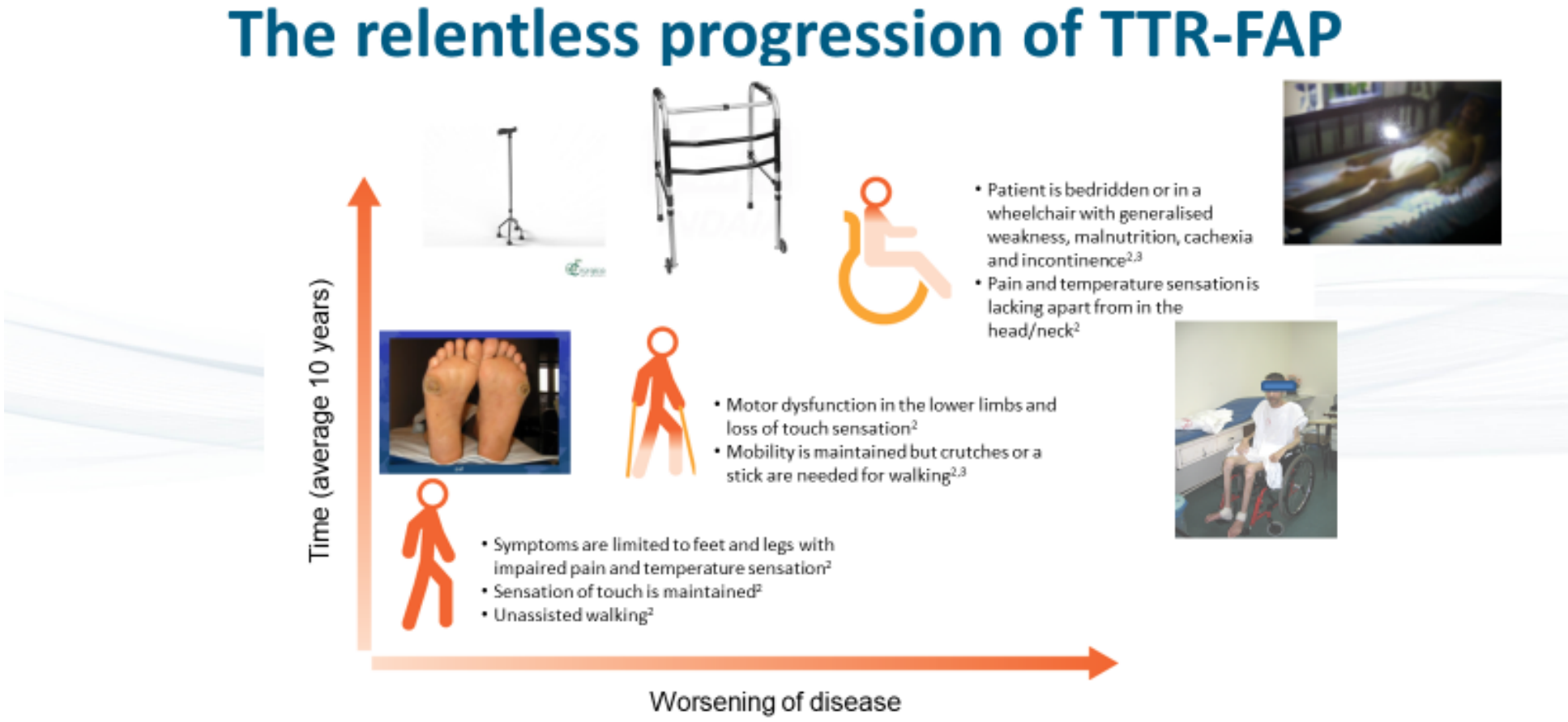
12/2004 Assymptomatic carrier

05/2006. Disease onset and diagnosis, PND =I.

Óbito em janeiro de 2016

07/2014.PND = IIIA

Coutinho stages

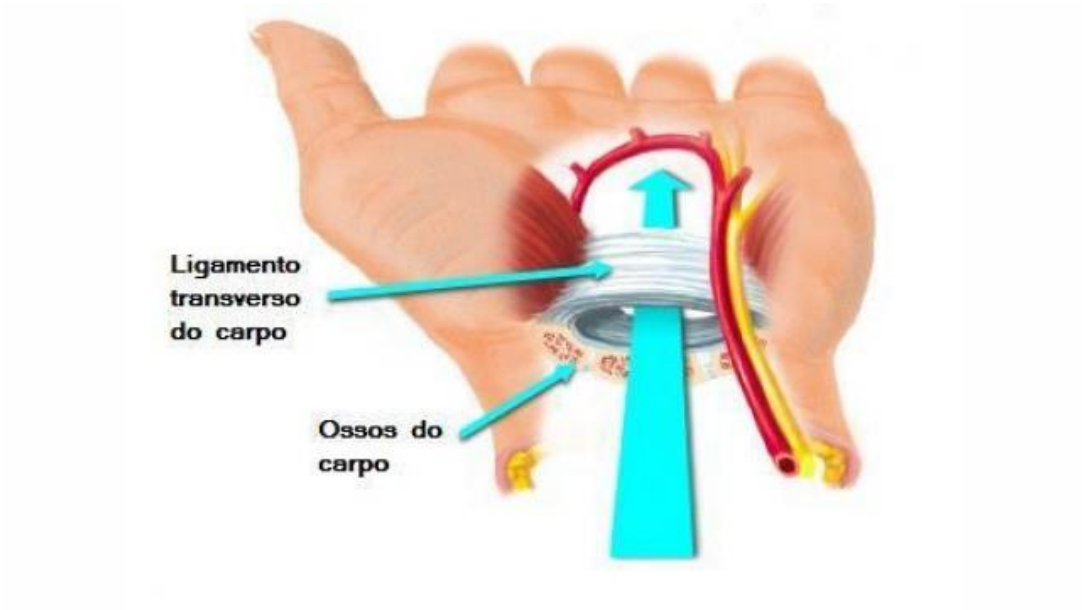


1.Hou X, et al. *FEBS J.* 2007;274:1637–50. 2
2. Coutinho P. In: Glenner GG *et al*, eds. *Amyloid and amyloidosis.* Amsterdam: Excerpta Medica, 1980.
3. Benson MD, et al. *Amyloid.* 1996;3:44–56.

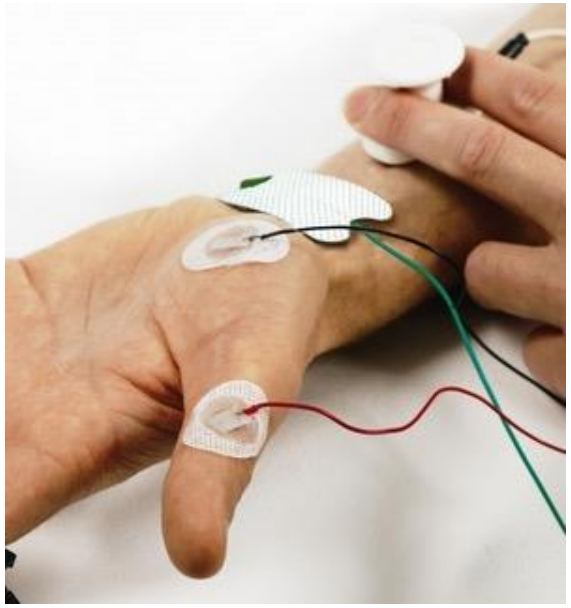
Carpal tunnel syndrome

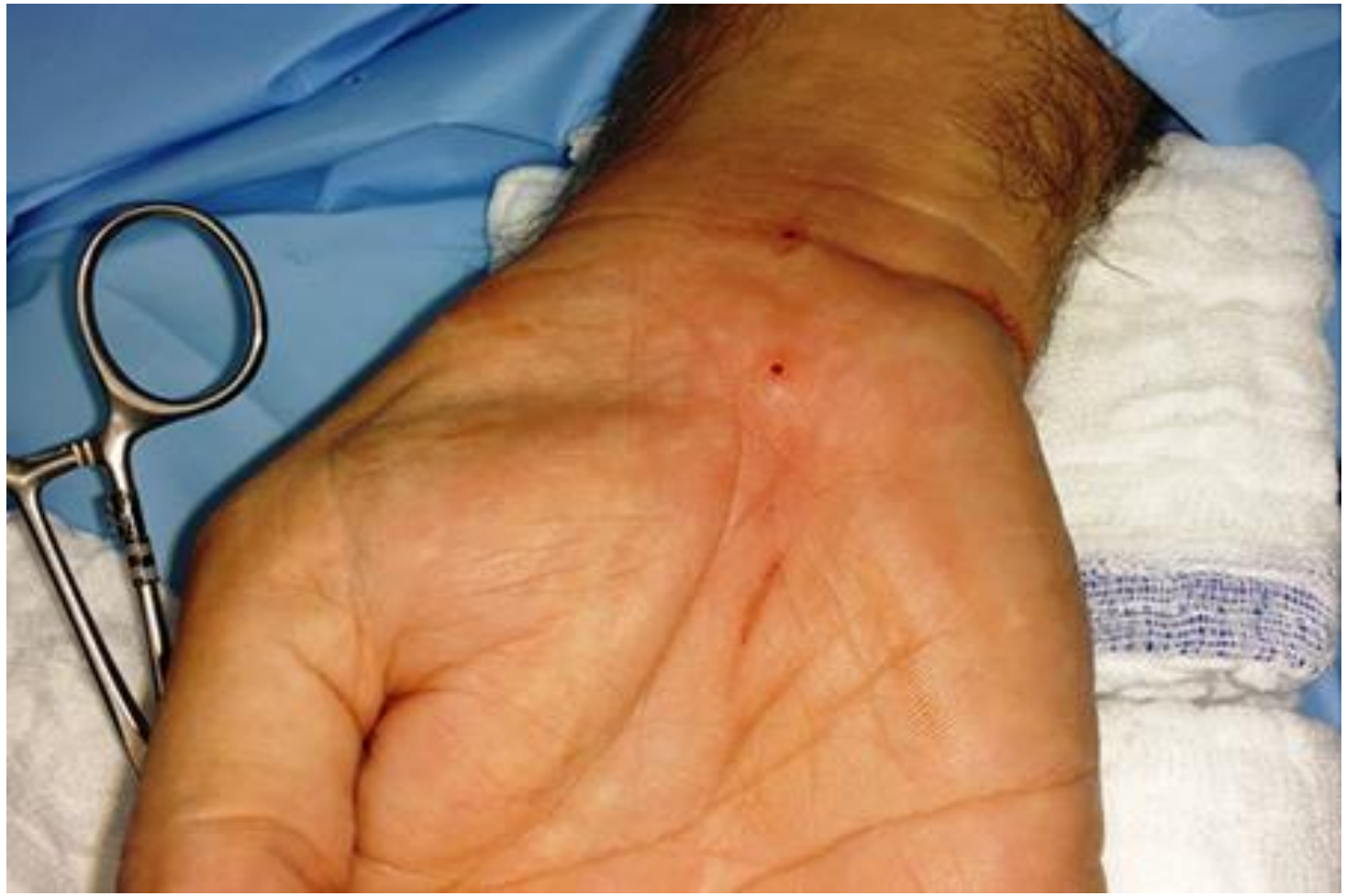
- Part of the Polyneuropathy.

- First presentation.



Carpal tunnel syndrome





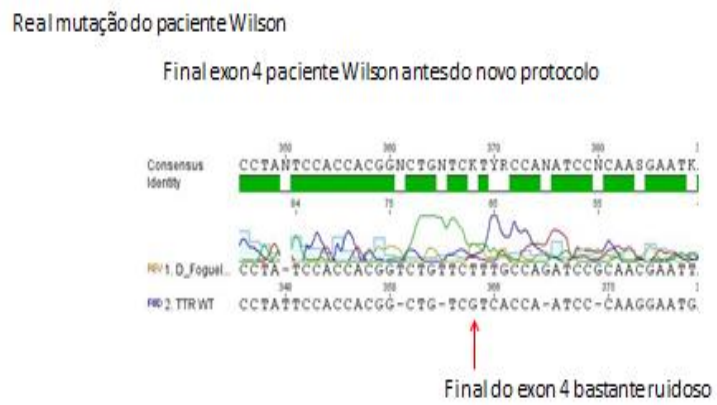
Is very frequent in the general population

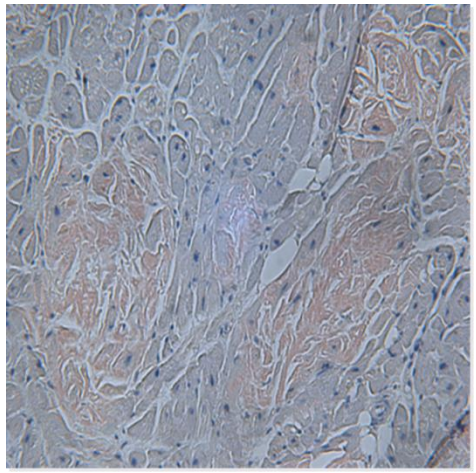
Case Study: Val122Ile in Brazil

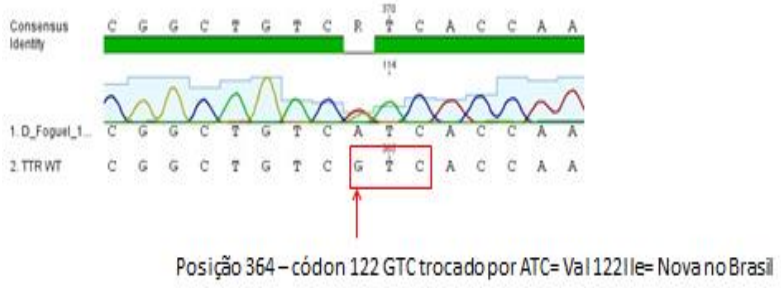
- Clinical course:
  - **Carpal Tunnel at 58**
  - **Cardiomyopathy** at 60
  - Disautonomia at 64
  - Dialysis at 65
- Cardiac biopsy: amyloid deposition
- No family history
- Origin: Portuguese **/ African**
- Rio de Janeiro

4% of African Americans may be carriers of Val122Ile *TTR* mutation

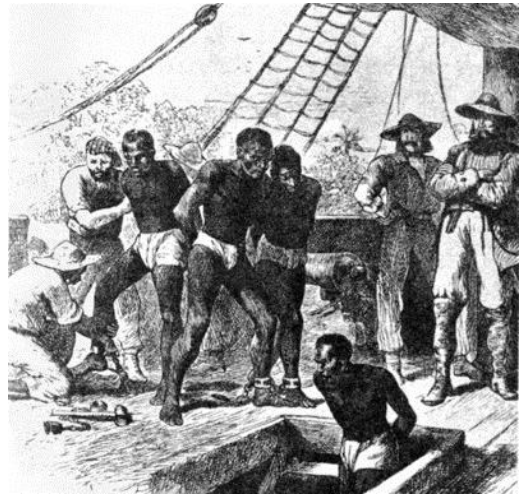
THAOS Brazil: n=3
THAOS Overall: n=78







Slavery. African origin of Americas.

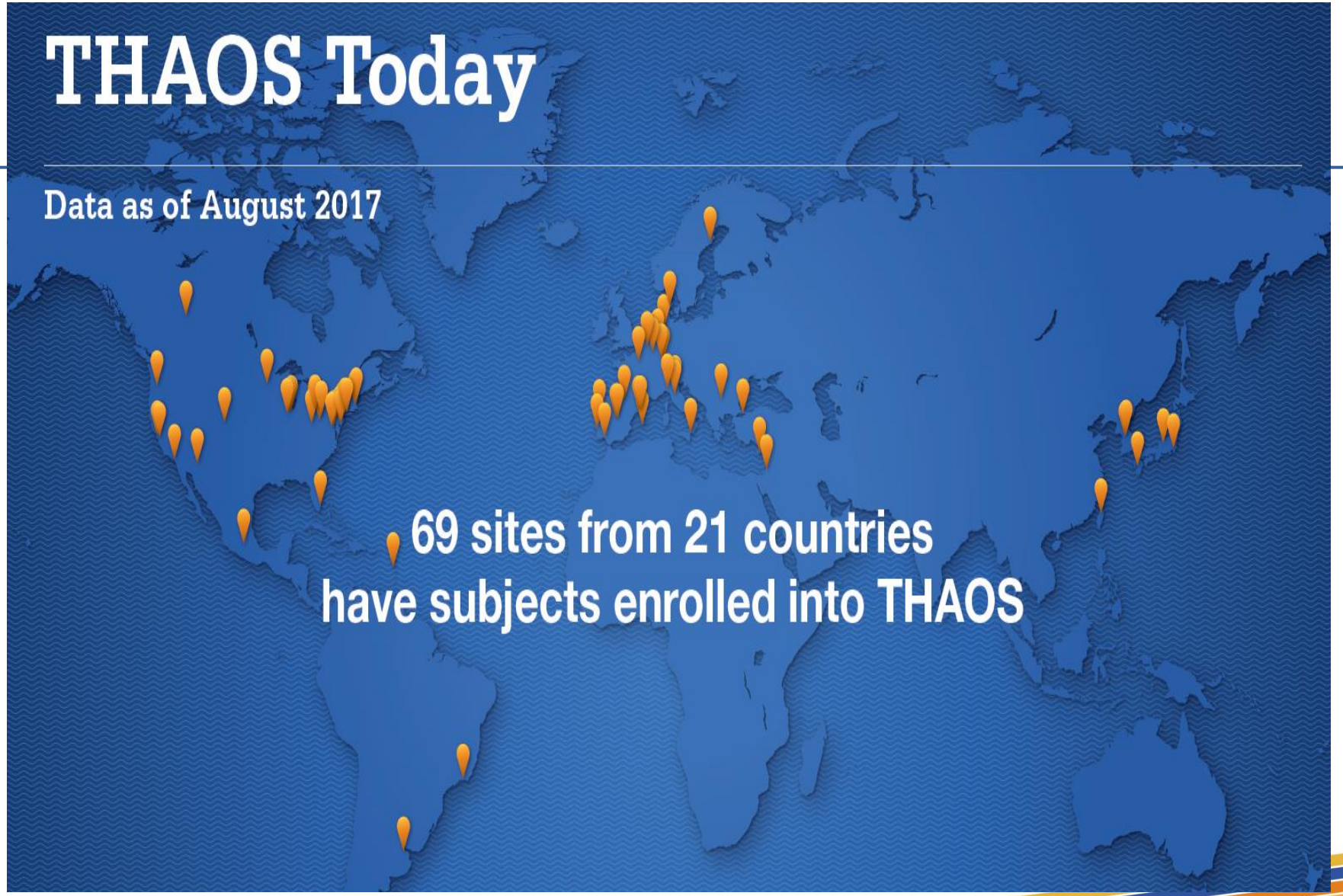


- 5 millions of slaves were brought to Brazil from West Africa (Angola) from 1551 to 1840.

- From XVI to XIX centuries 10 millions of slaves were sold to Americas. 40 % of this total came to Brazil.

THAOS Today

Data as of August 2017



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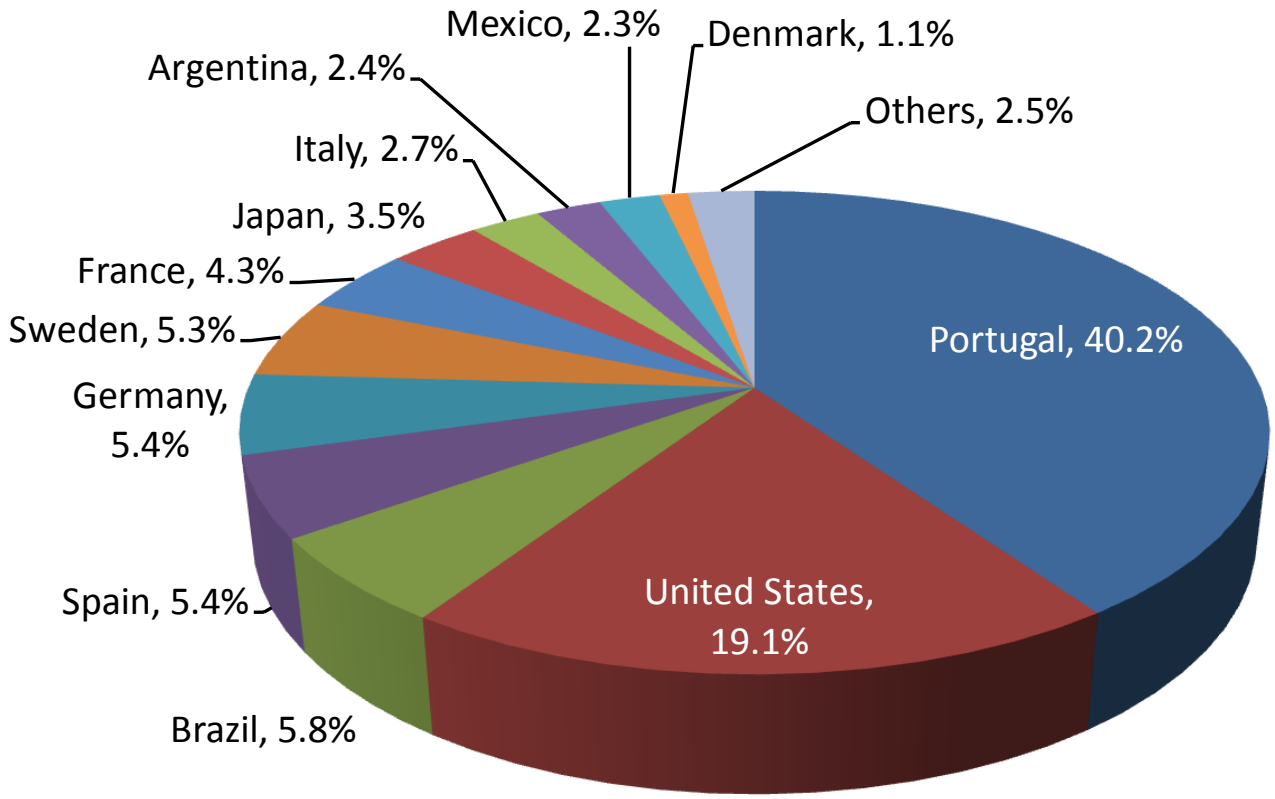
Transthyretin Amyloidosis Outcomes Survey

Countries and contributions to THAOS (%): 21 countries, 3,399 subjects



Others:
- Belgium
- Bulgaria
- Canada
- Cyprus
- Israel
- Netherlands
- South Korea
- Taiwan
- Turkey

Data as of 01 August 2017

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Most Common *TTR* Mutations 2017 (101 unique mutations in 2930 subjects)

Mutation	Total	% of patients with TTR mutation	Cumulative %
Val30Met	2138	73.0%	73.0%
Val122Ile	160	5.5%	78.4%
Thr60Ala	69	2.4%	80.8%
Ser50Arg	68	2.3%	83.1%
Glu89Gln	62	2.1%	85.2%
Phe64Leu	36	1.2%	86.5%
Ser77Tyr	28	1.0%	87.4%
Ile107Val	24	0.8%	88.2%
Gly47Ala	22	0.8%	89.0%
Val20Ile	20	0.7%	89.7%
Leu111Met	19	0.7%	90.3%
Glu89Lys	14	0.5%	90.8%
Val28Met	13	0.4%	91.2%
DelVal122	11	0.4%	91.6%
Ser52Pro	10	0.3%	92.0%

Heterozygous:58 subjects

85 different mutations reported in 9 or fewer patients

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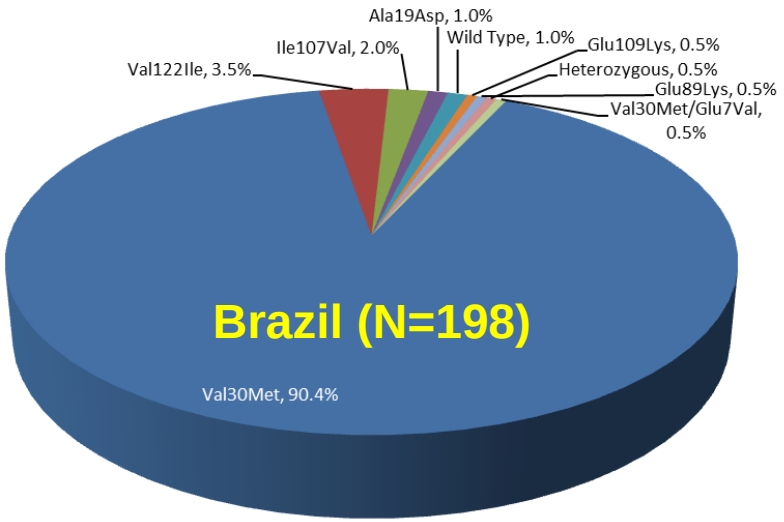
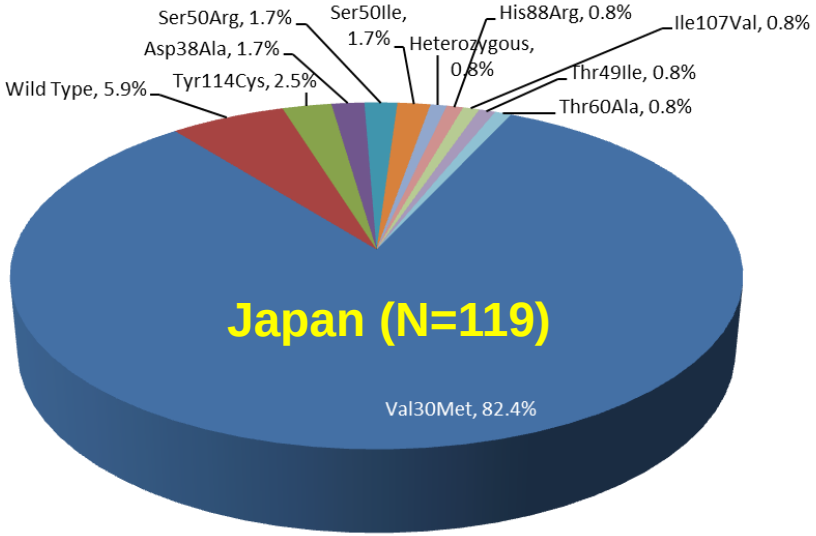
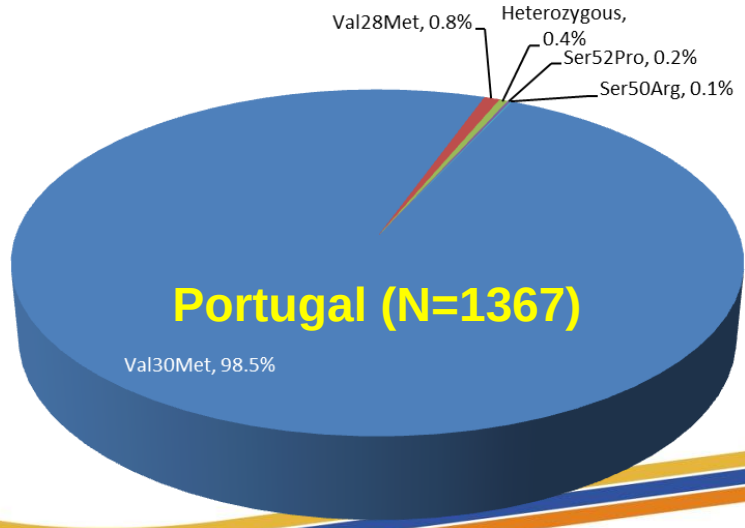
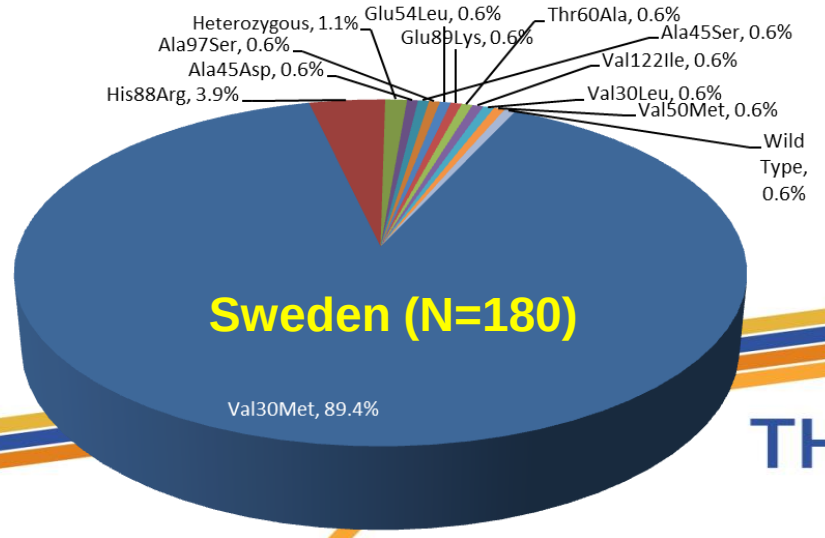
Genotypic Spectrum in "V30M endemic" Regions









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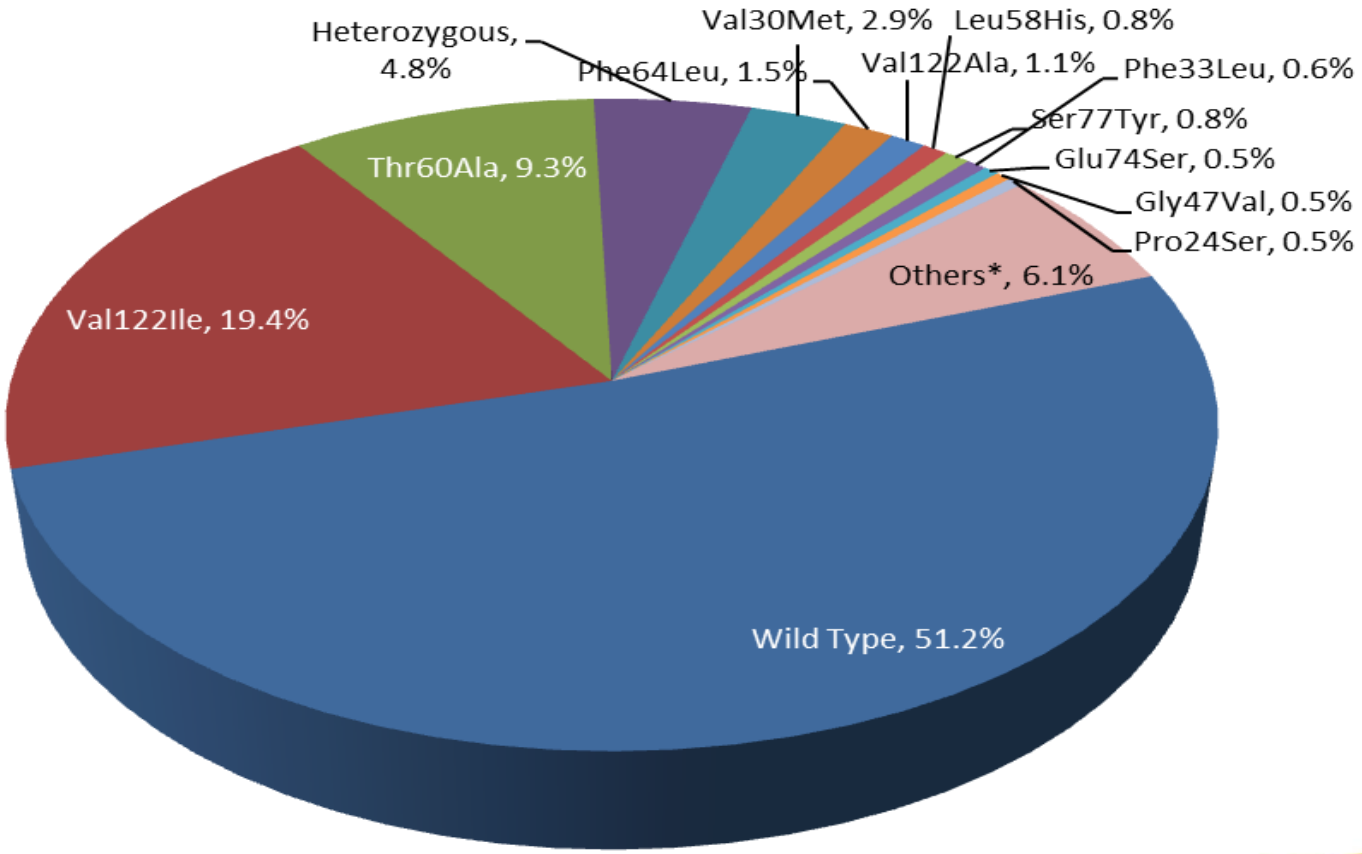
Spectrum of Mutations in USA
N=648



*Other 33 mutations affecting 40 patients

Data as of 01 August 2017

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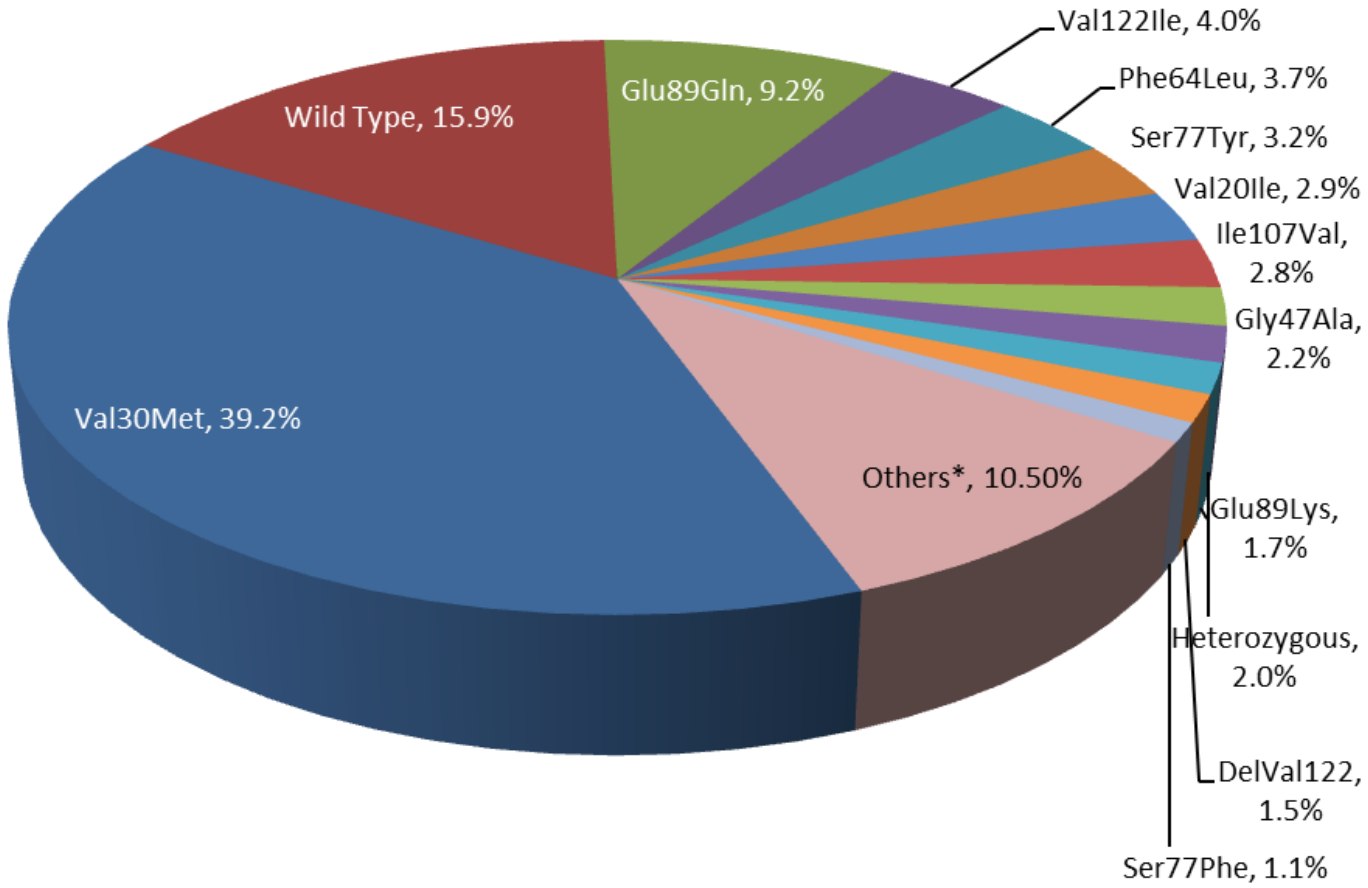
Spectrum of Mutations in Europe
(excluding Portugal and Scandinavia) N=650



*Other 42 mutations affecting 69 patients

Data as of 01 August 2017

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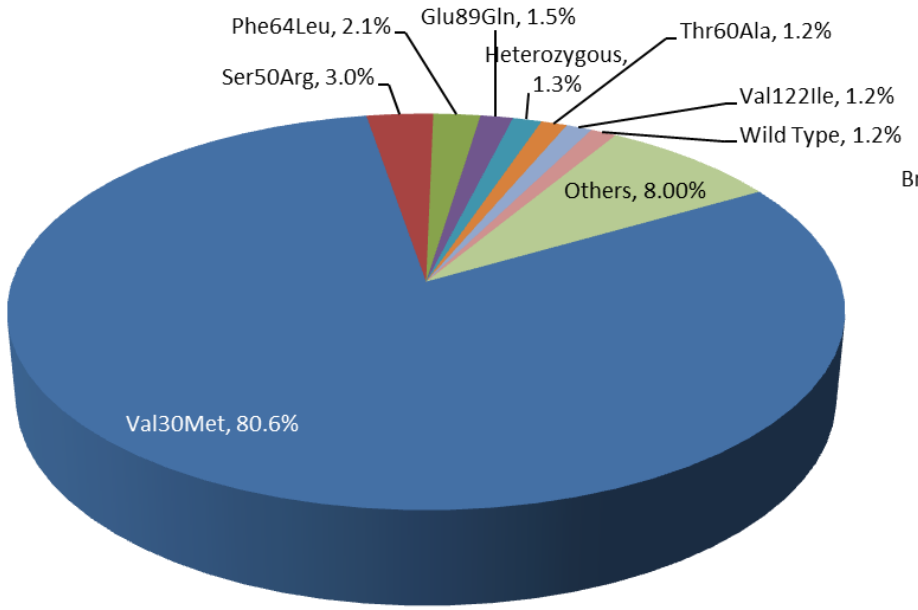
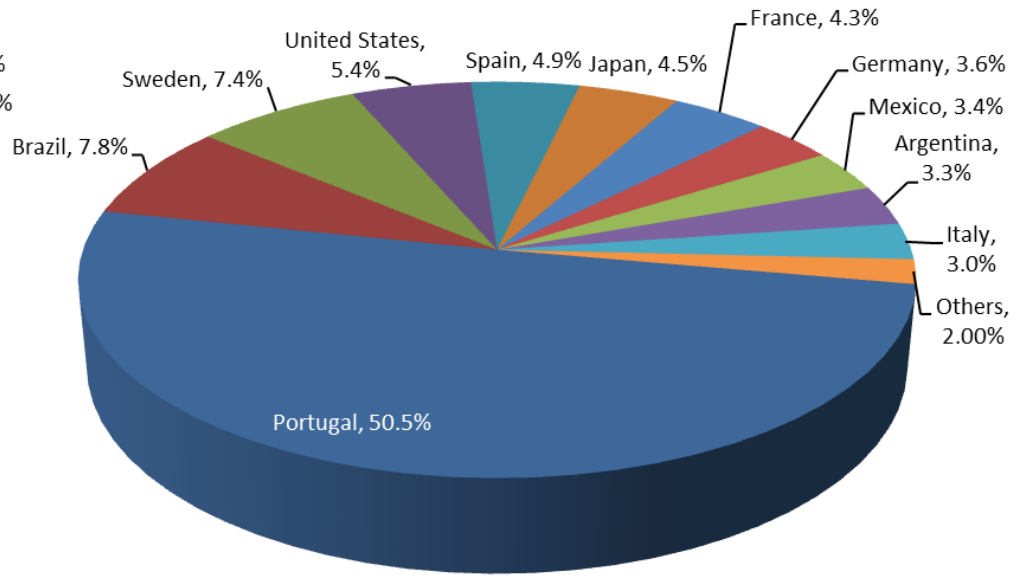
Neurologic Phenotype (%)
N=1381

Genotype



Geography



Data as of 01 August 2017

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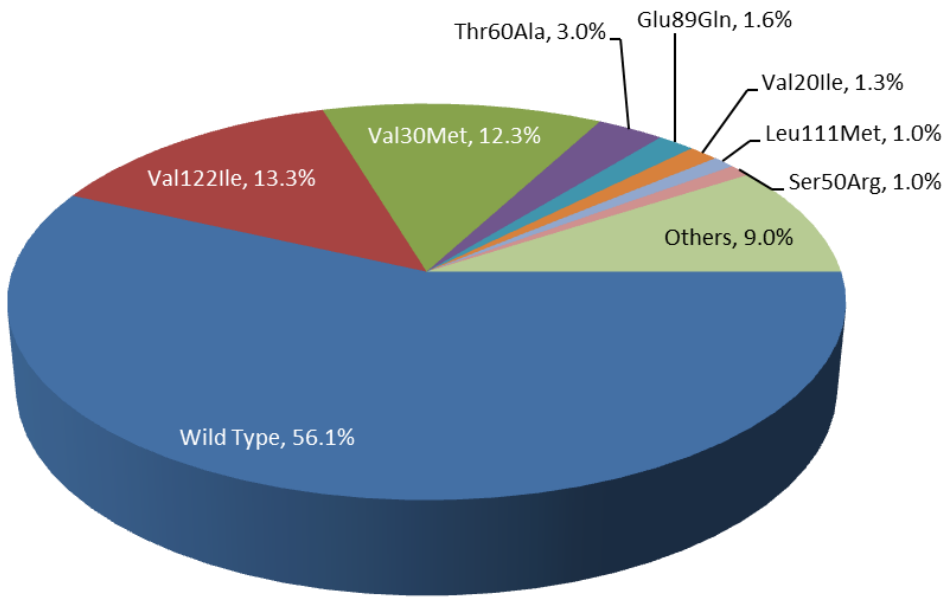
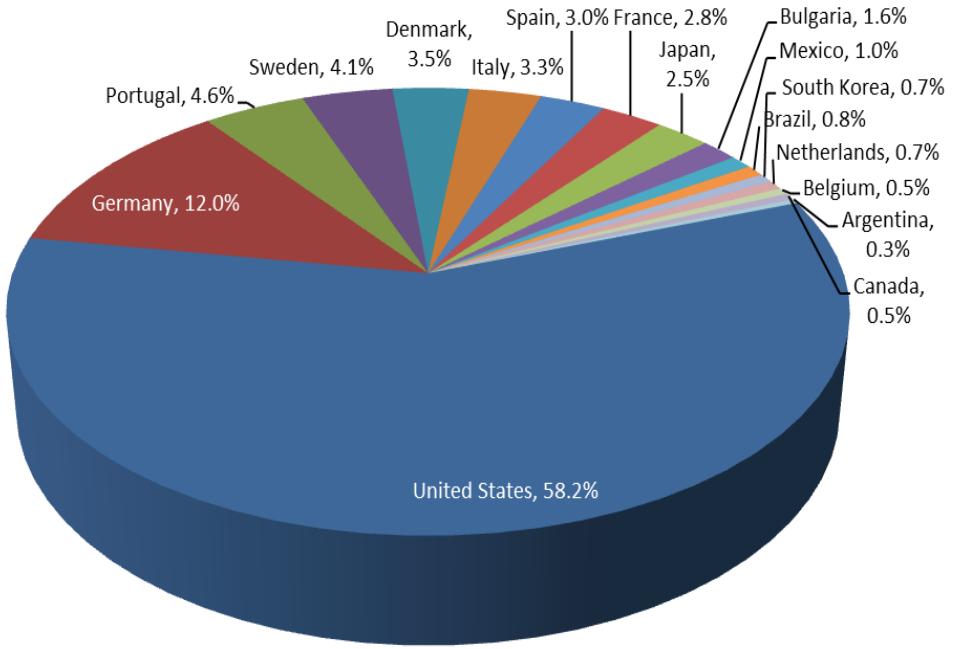
Cardiac Phenotype (%)
N=608

Genotype



Geography



Data as of 01 August 2017

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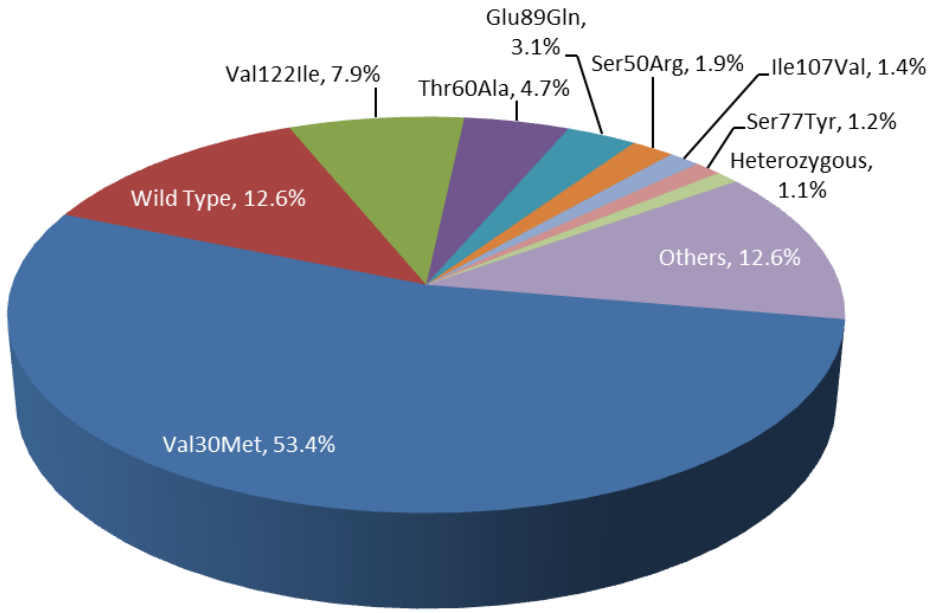
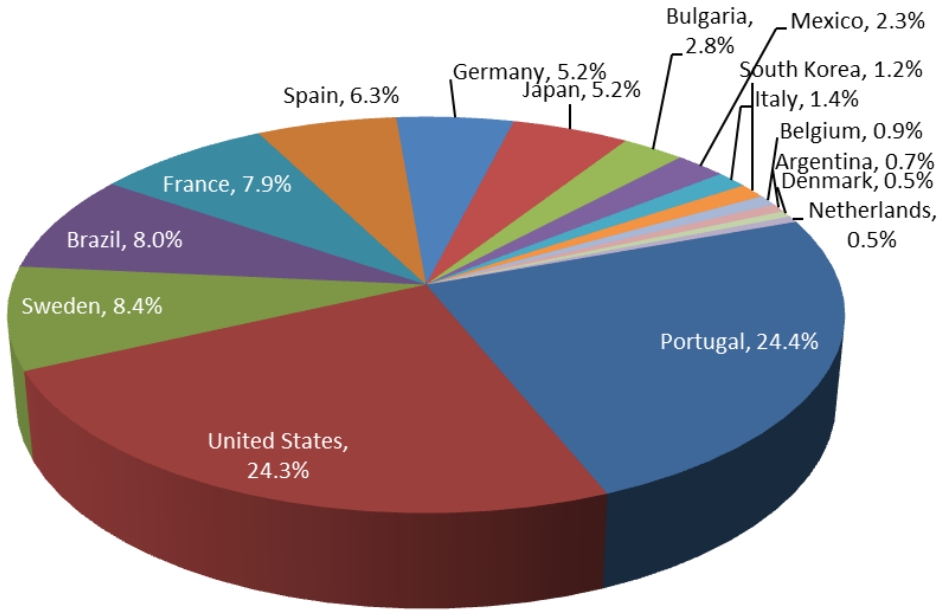
Mixed Phenotype (%)
N=573

Genotype



Geography



Data as of 01 August 2017

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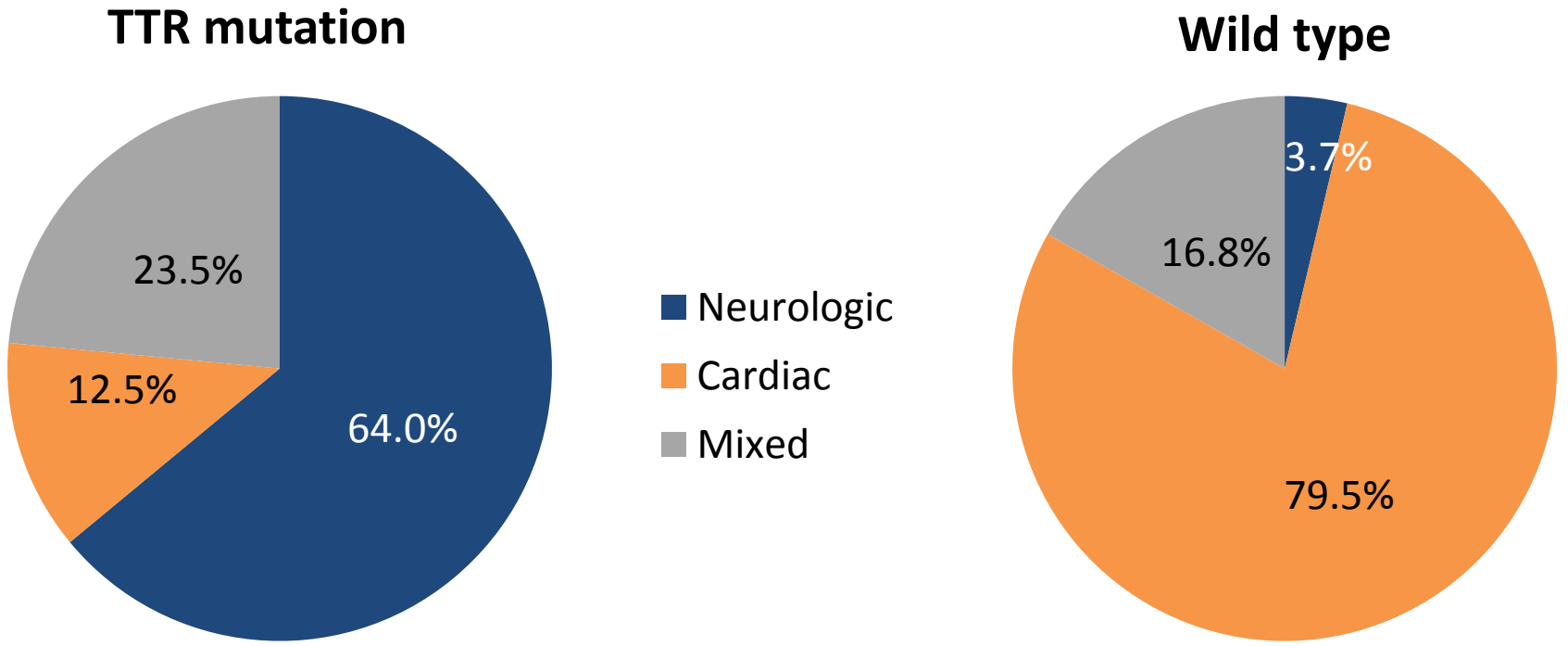
Distribution of phenotypes



Data as of 01 August 2017

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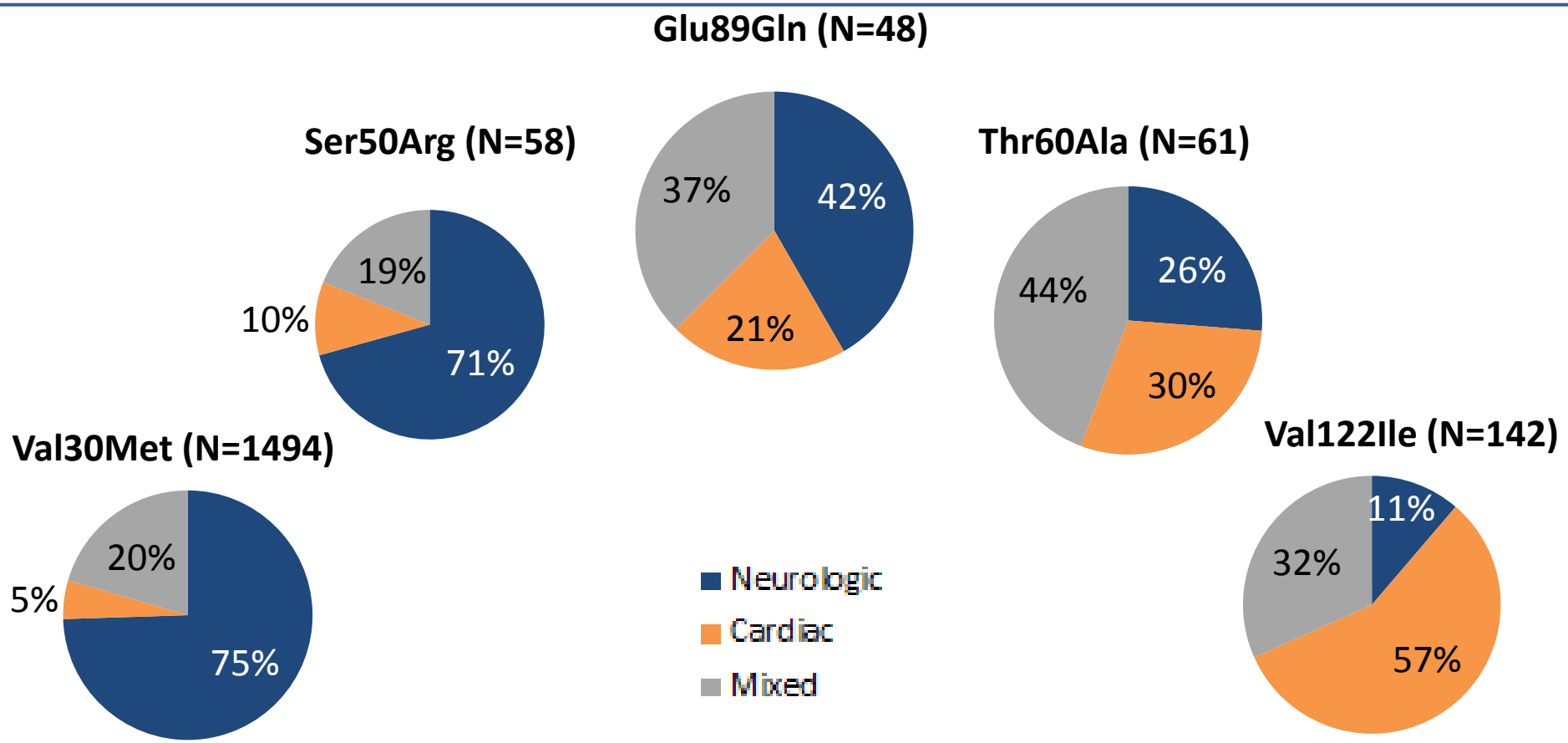
Distribution of phenotypes (main genotypes)



Data as of 01 August 2017

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Summary

- 4% of wild-type symptomatic subjects presented as neurologic phenotype
- 5% of symptomatic Val30Met subjects presented as cardiologic phenotype, and 11% of Val122Ile subjects presented as neurologic phenotype

What can be done

- Nice neurological examination.
- NC
- SSR and other autonomic tests
- QST
- HRDB
- Biopsies
- Recognize disease

- Treat disease. Treat pain.
- Care and prevention of wounds, burnings.


#Pausa no PAF