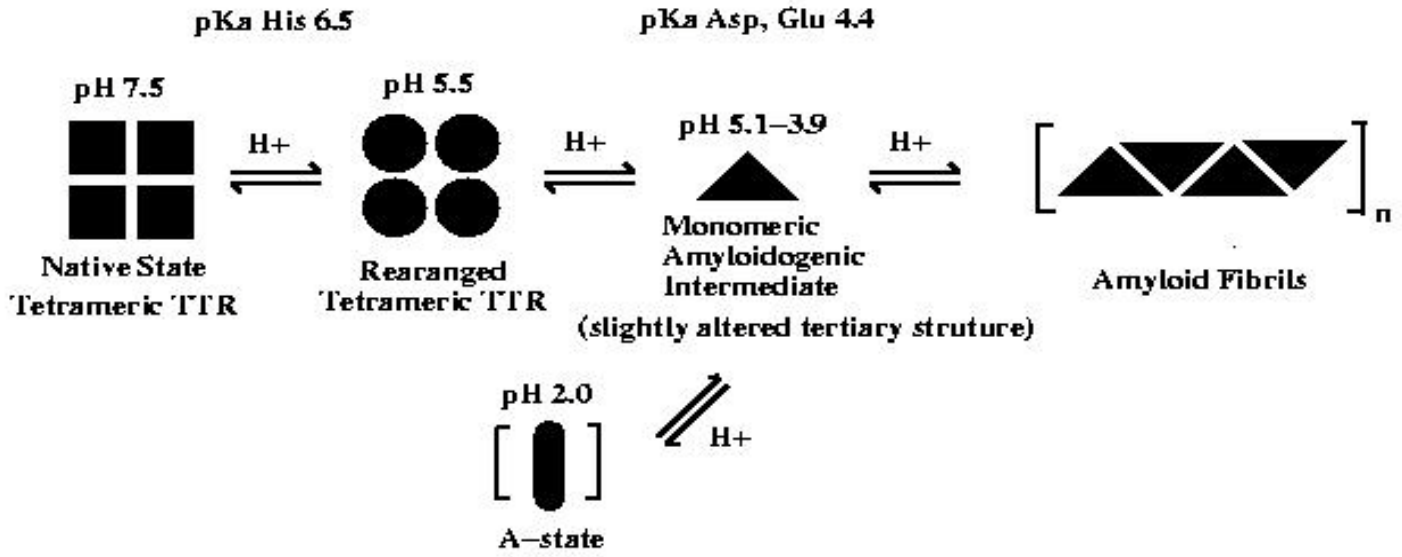
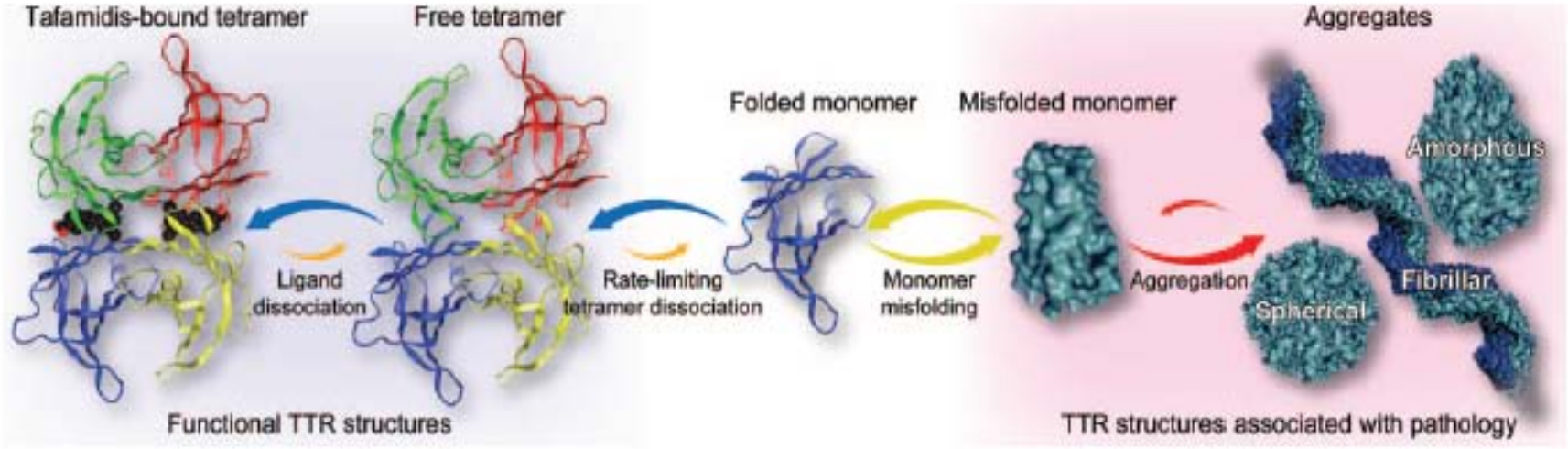
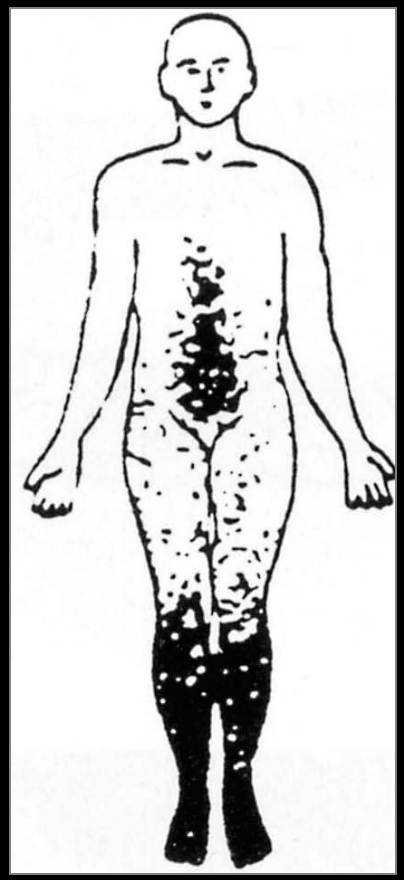
TranstHyretin Amyloidosis Outcome Survey

Agenda:

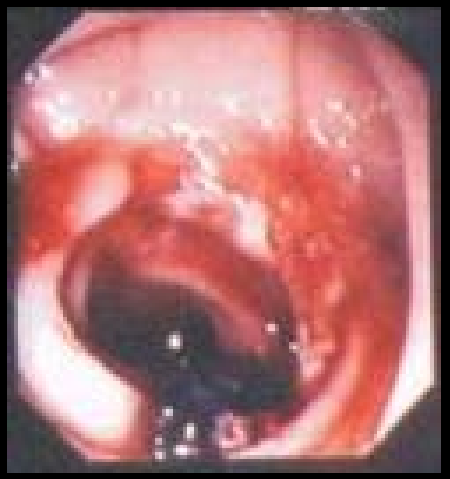
- What is ATTR ?
- What is THAOS ?
- How can we use THAOS to expand our knowledge of ATTR-related amyloidosis and to improve diagnosis and management ?


pKa His 6.5
pKa Asp, Glu 4.4
pH 7.5
pH 5.5
pH 5.1–3.9
H+
H+
H+
Native State
Tetrameric TTR
Rearanged
Tetrameric TTR
Monomeric
Amyloidogenic
Intermediate
(slightly altered tertiary struture)
Amyloid Fibrils
n
pH 2.0
H+
A–state


Tafamidis-bound tetramer
Free tetramer
Aggregates
Folded monomer
Misfolded monomer
Amorphous
Ligand
dissociation
Rate-limiting
tetramer dissociation
Monomer
misfolding
Aggregation
Spherical
Fibrillar
Functional TTR structures
TTR structures associated with pathology

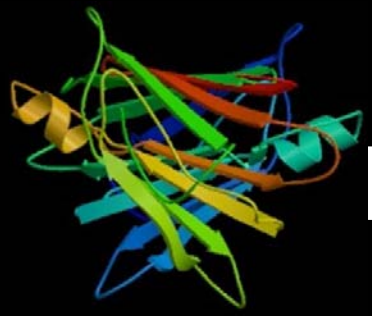


MUTATED
ATTR



“Senile Systemic Amyloidosis” (wt ATTR-related Amyloidosis)

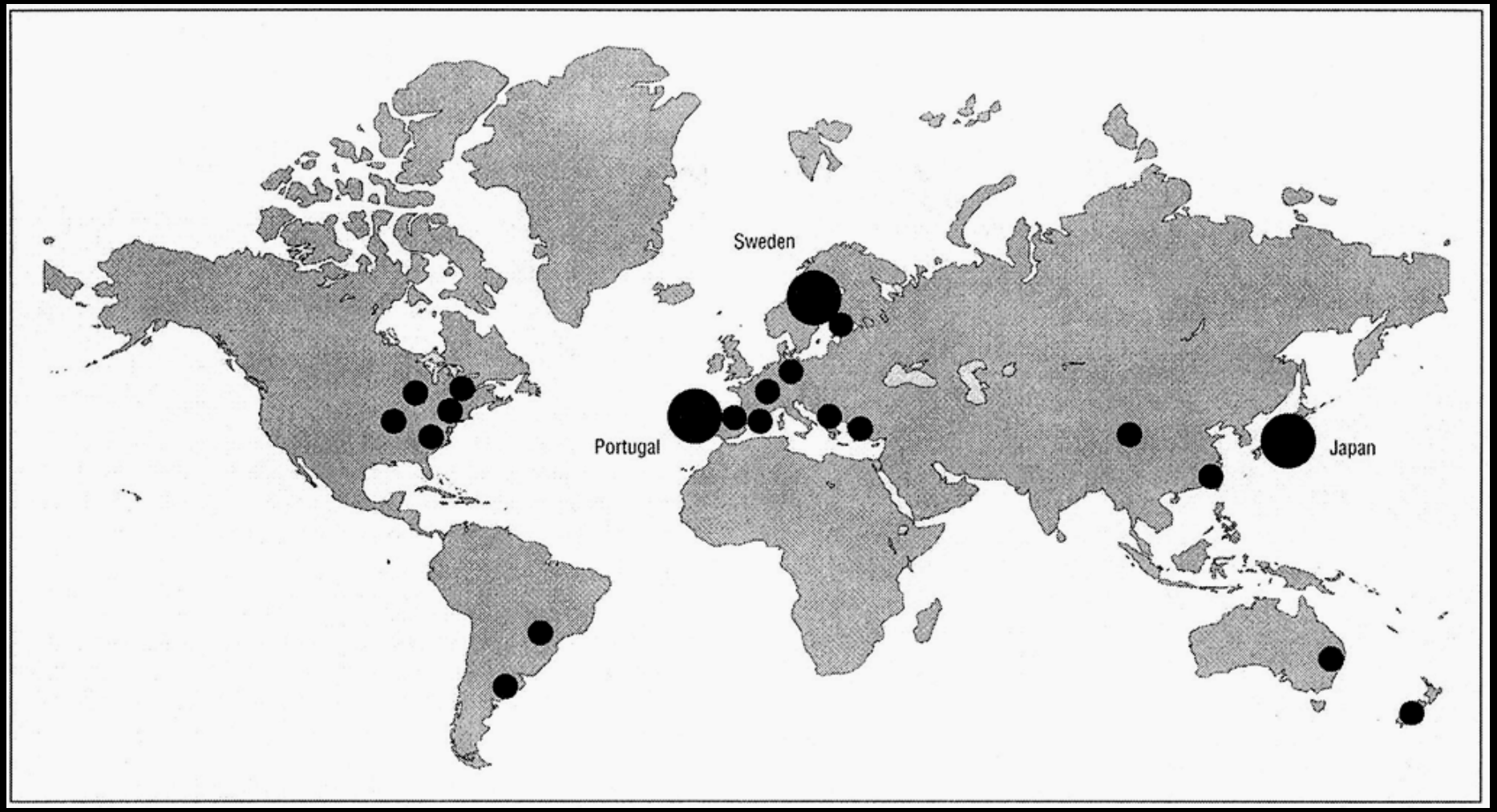
100 %



wild-type ATTR

50 %

Familial ATTR across the world

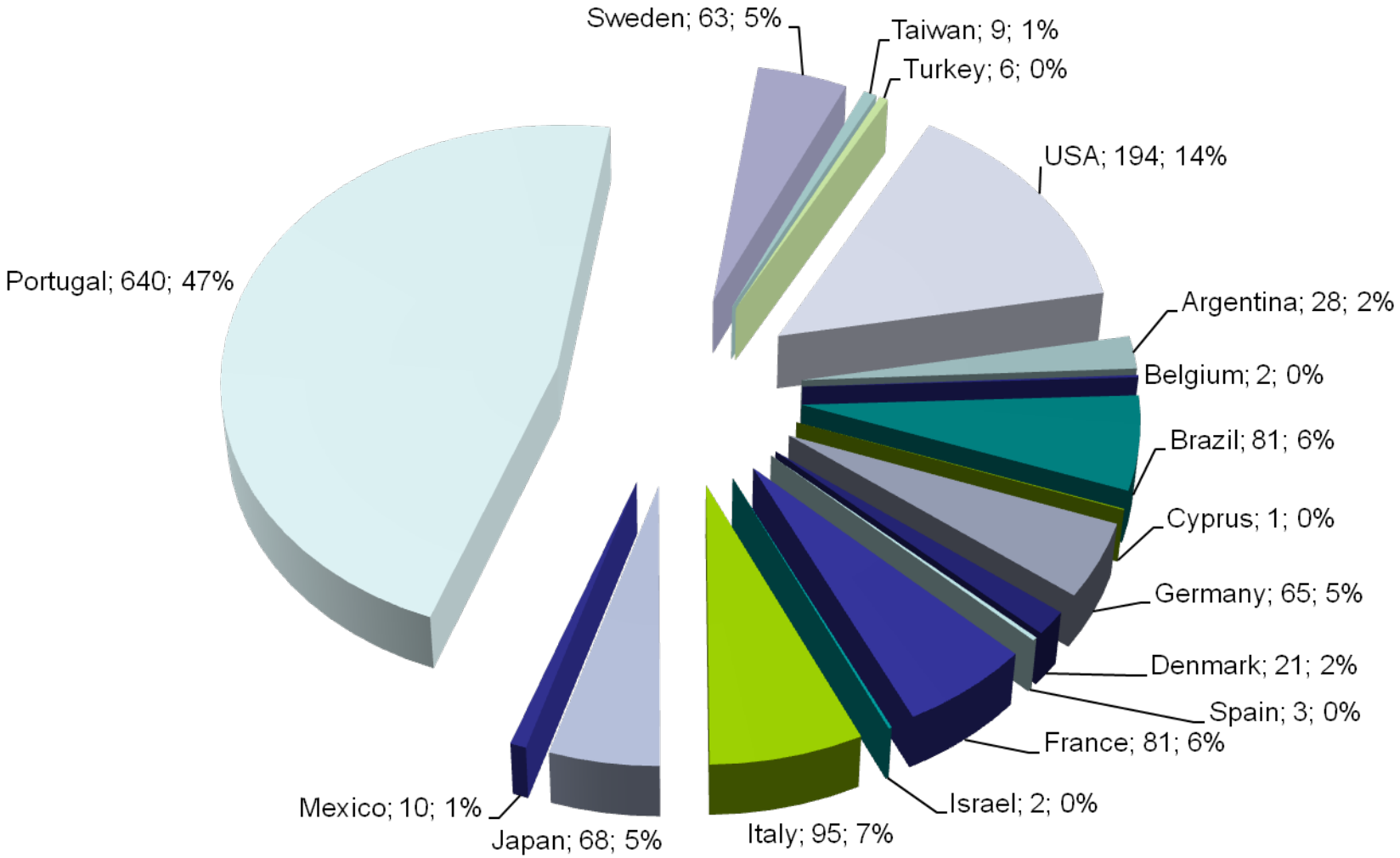


TranstHyretin Amyloidosis Outcome Survey

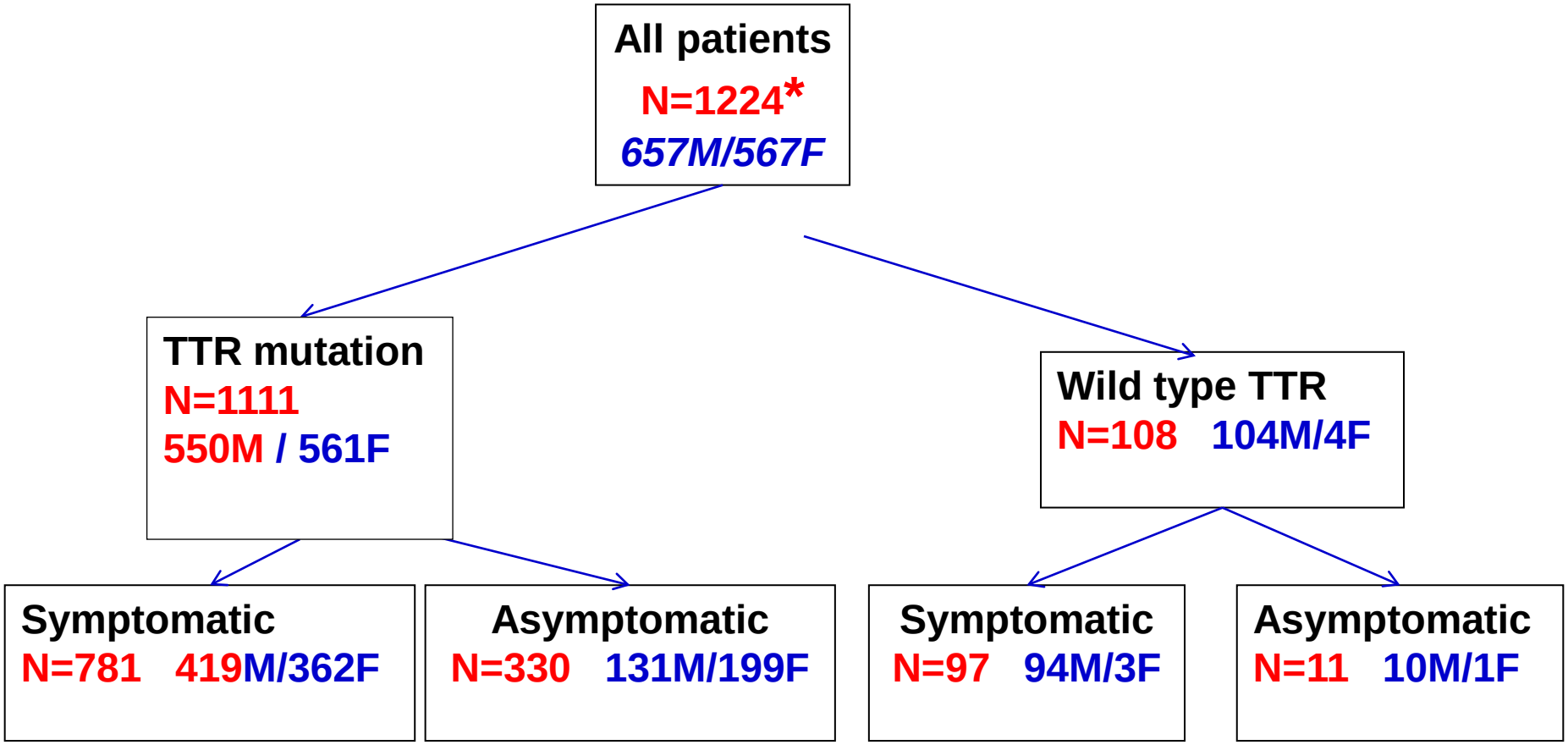
- **Worldwide, longitudinal, observational survey**
- **Symptomatic individuals with wild type or variant ATTR and asymptomatic carriers**
- **To study differences in disease presentation, diagnosis, and natural history in geographically dispersed populations**
- **Sponsored by Pfizer Inc. and overseen by an independent Scientific Board**
- **Since 2007: 1366 individuals from 47 sites in 19 countries enrolled (current analysis referred to 1224 subjects for demographics and to subsets of different size for other variables according to available validated data)**

1366 subjects from 47 sites in 19 Countries

June 2012

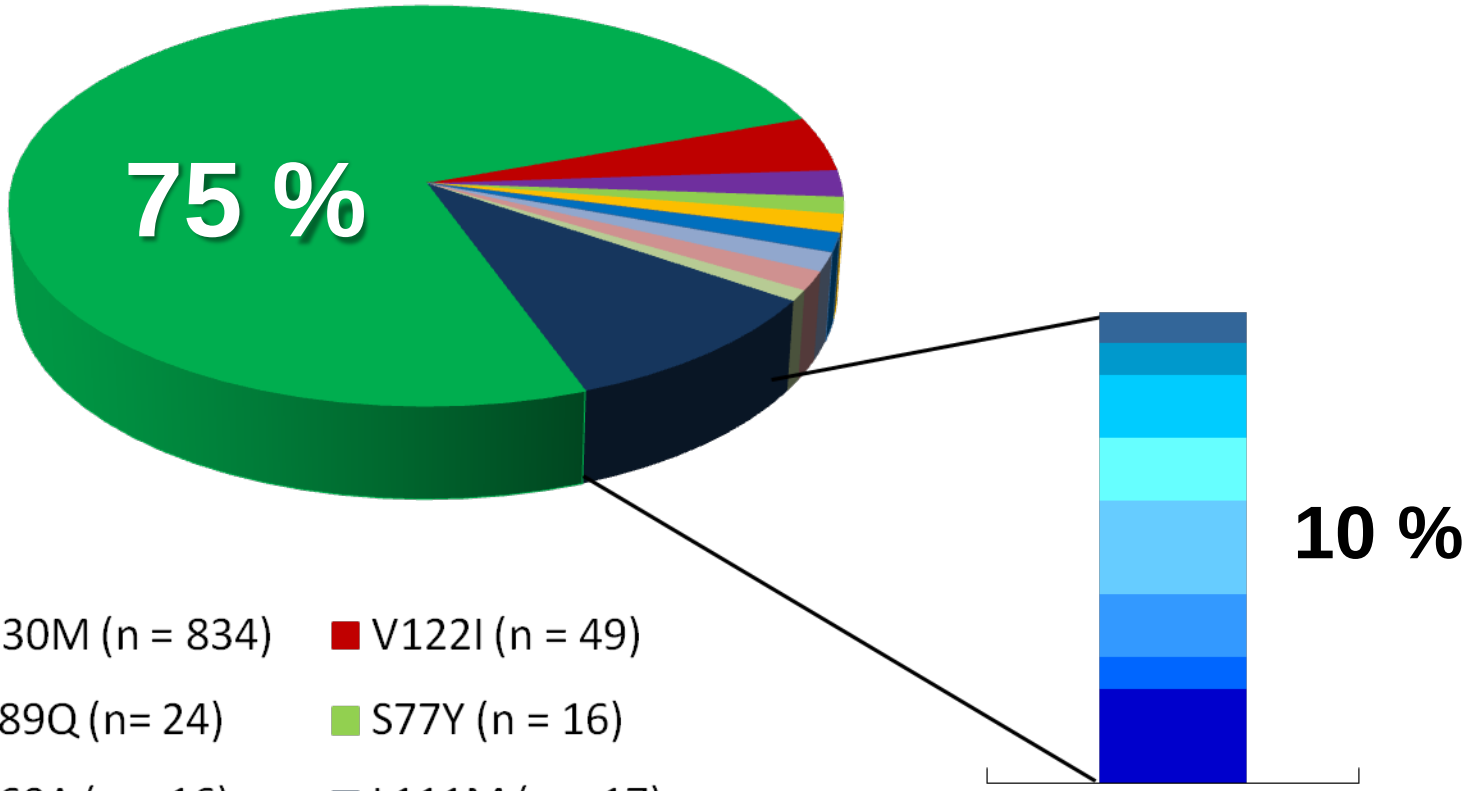


THAOS: validated and analyzed data



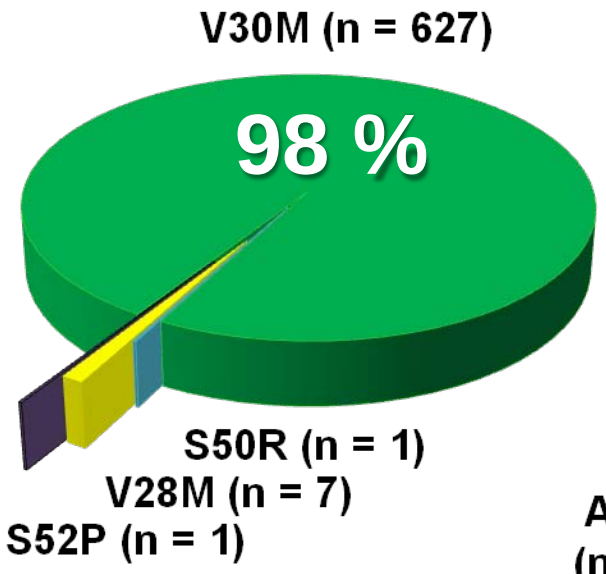
*5 Patients (3M/2F) with Polymorphism are not included above

Worldwide Genotypic Spectrum
1111 subjects

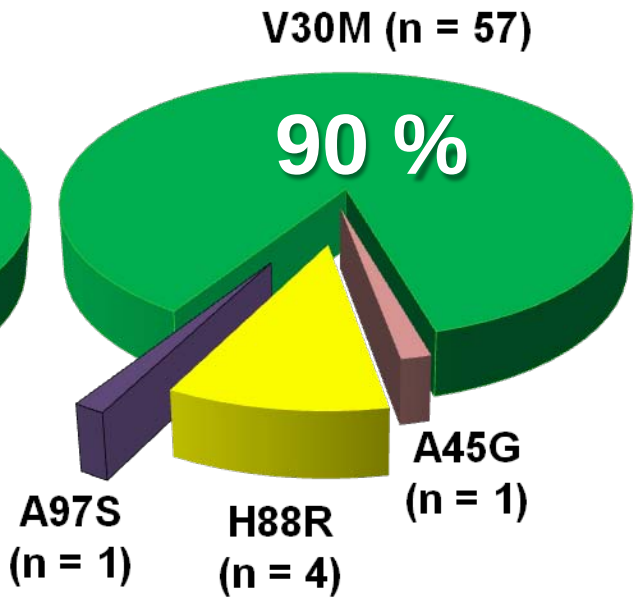


Genotypic Spectrum

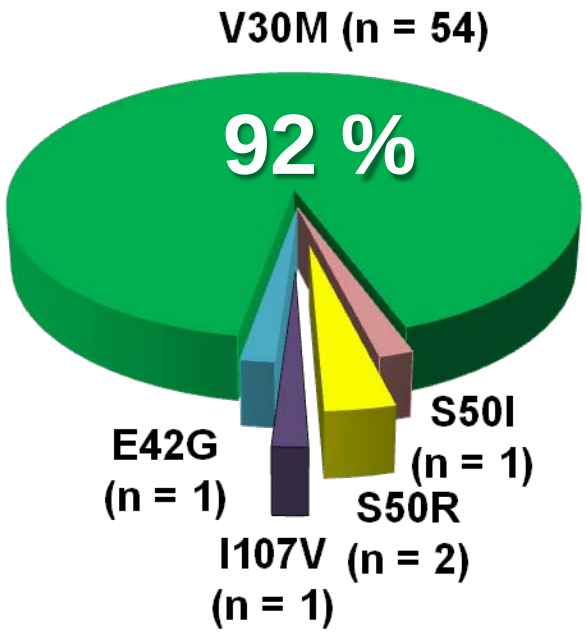
Portugal n= 636



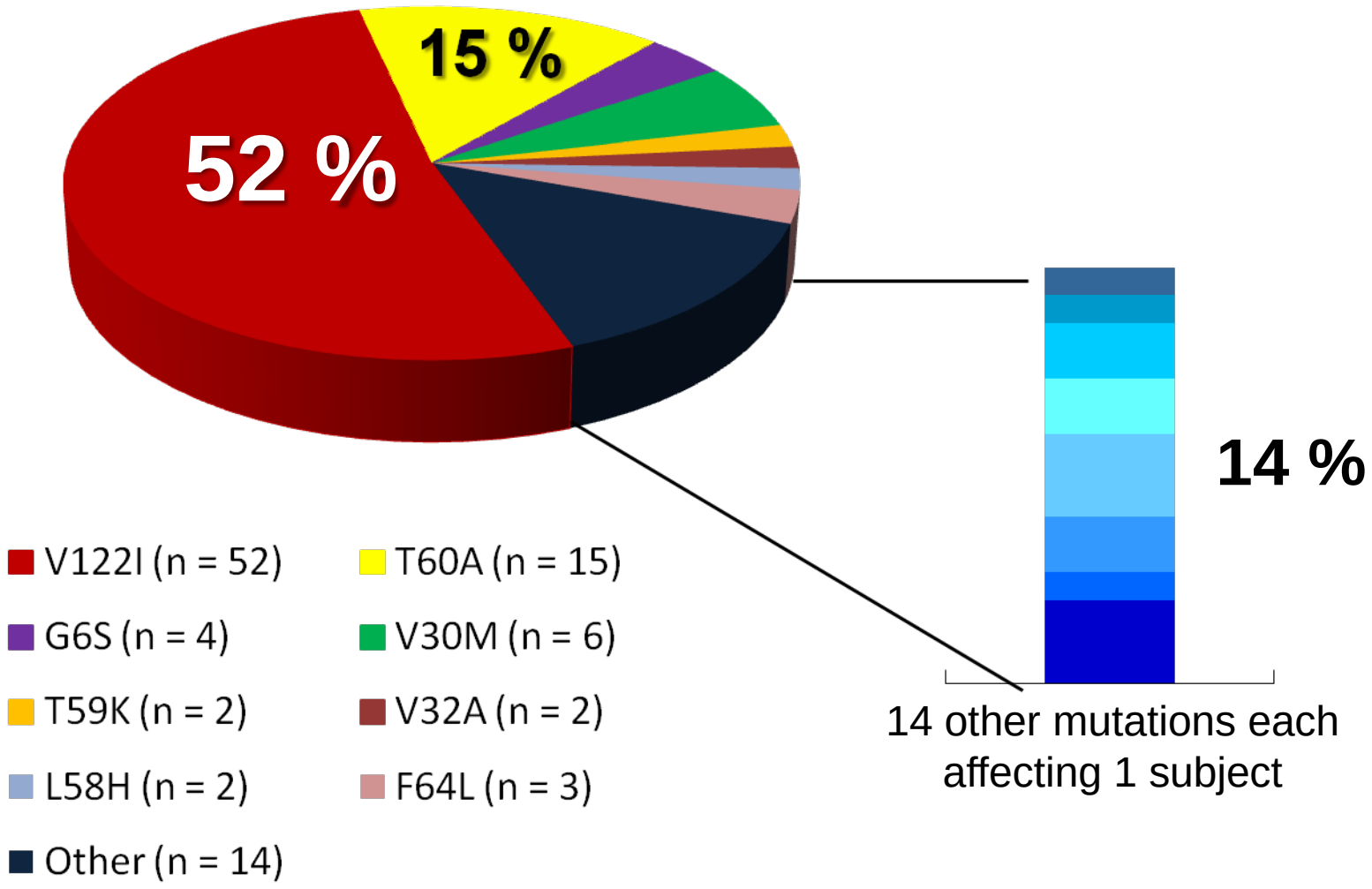
Sweden n= 63



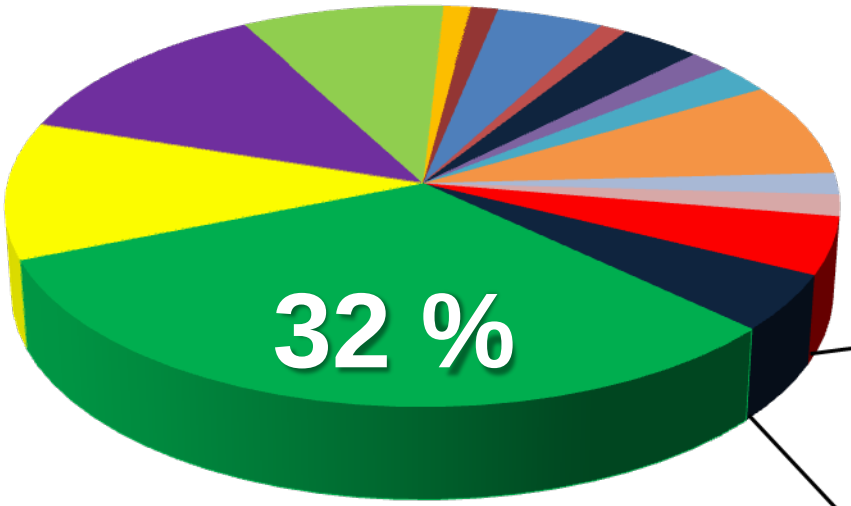
Japan n= 59

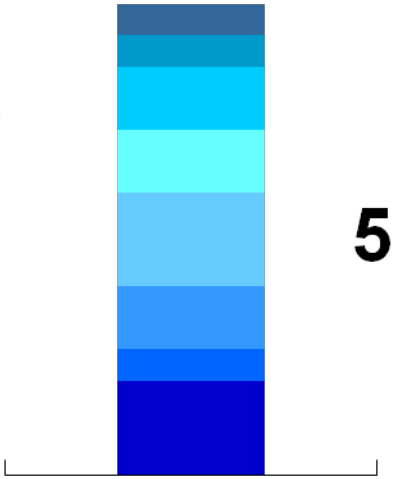


Genotypic Spectrum, USA n =100



Genotypic Spectrum, Western Europe
Excluding Portugal and Scandinavia (and UK) n= 172

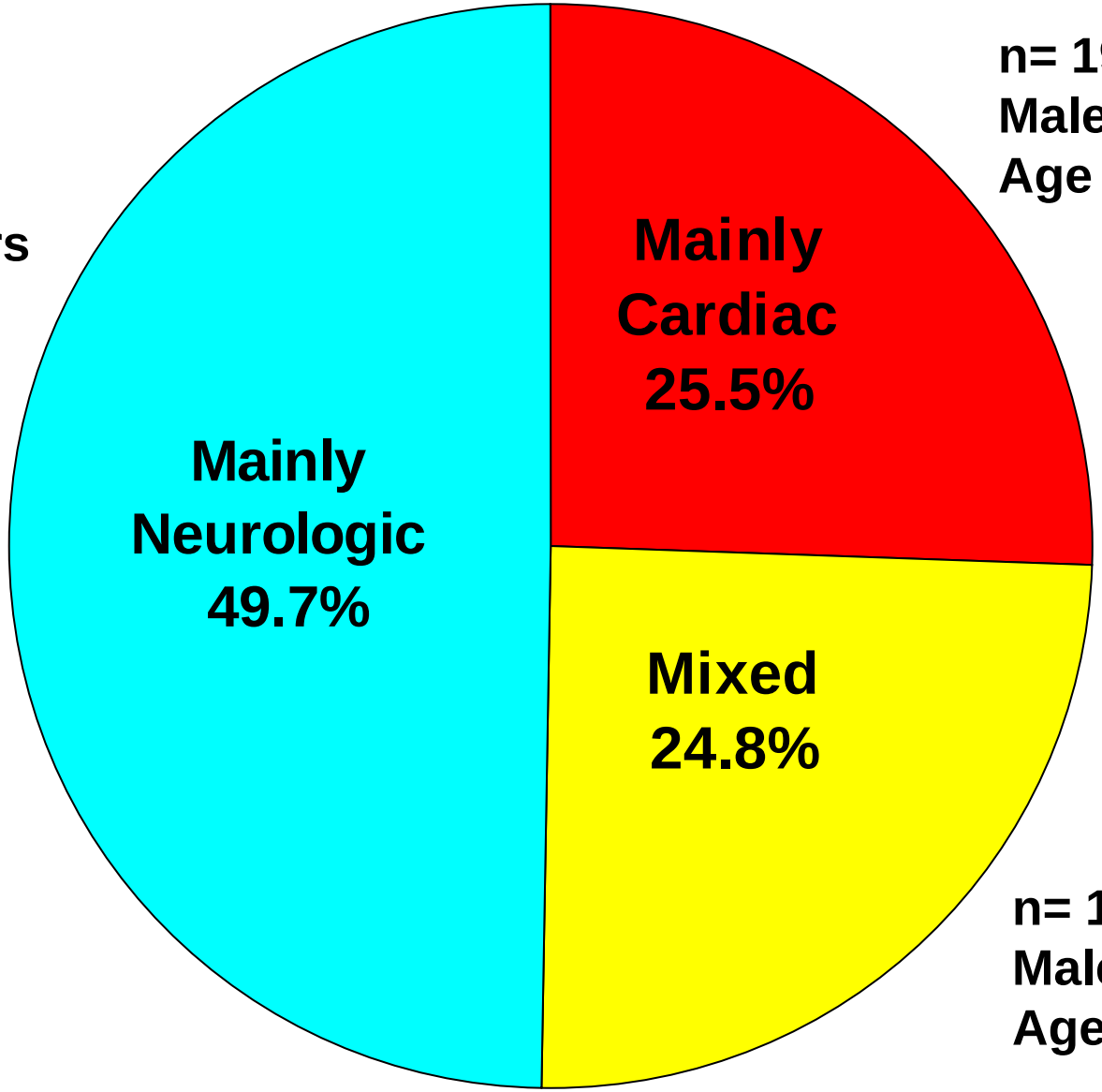




- V30M (n = 55)
- E89Q (n = 21)
- E89L (n = 2)
- T49A (n = 8)
- I107V (n = 6)
- S77F (n = 4)
- Y116S (n = 3)
- V120I (n = 8)
- I68L (n = 19)
- F64L (n = 15)
- G47A (n = 2)
- T59L (n = 2)
- S50R (n = 3)
- S77Y (n = 13)
- V122I (n = 3)
- Other (n = 8)

8 other mutations each affecting 1 subject

Clinical Phenotypes at Presentation Among 776 symptomatic TTRm pts

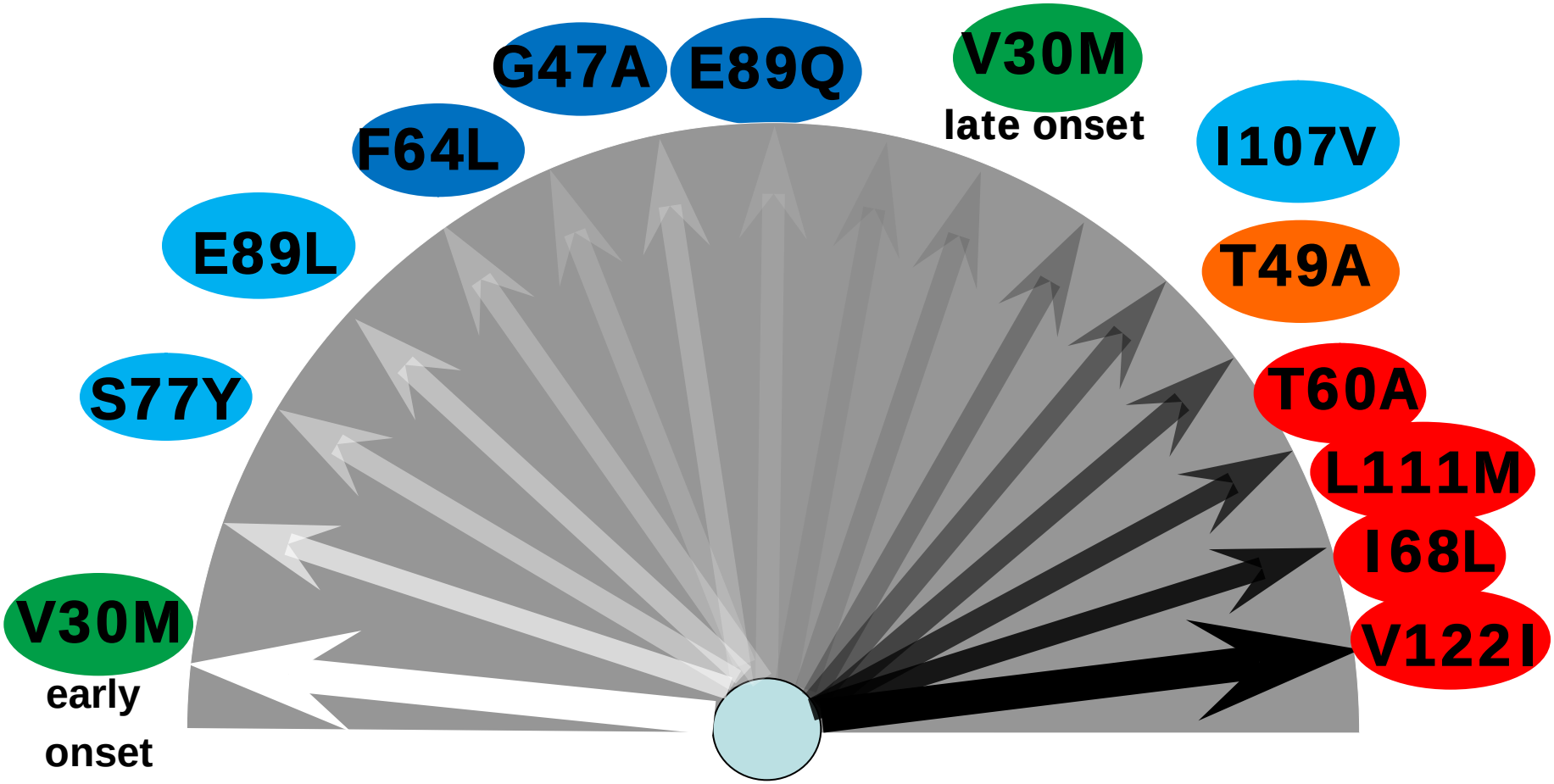


n= 198
Male 74%
Age 62 ±12 yrs

n= 385
Male 50.5%
Age 46 ±14 yrs

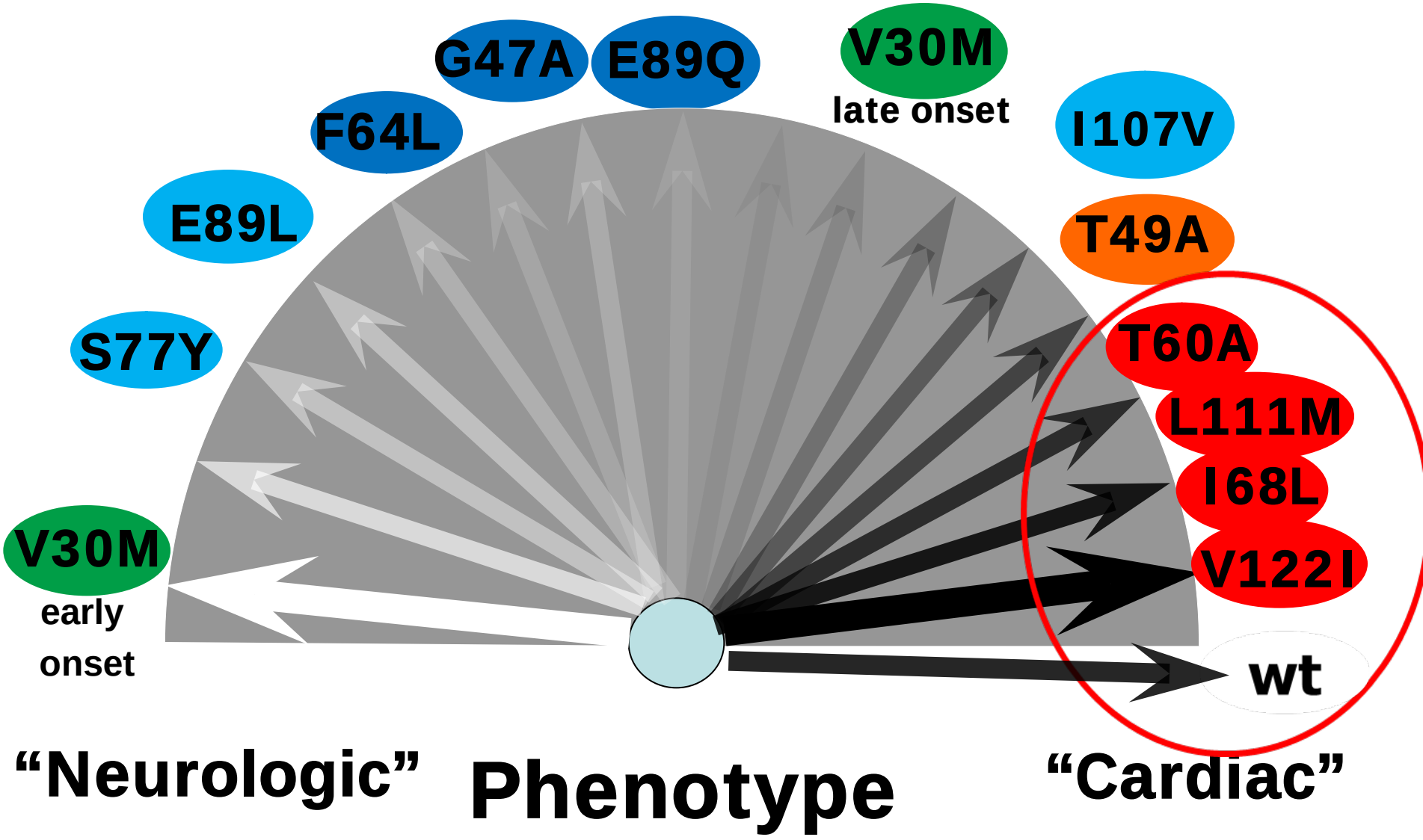
n= 193
Male 39%
Age 42 ±13 yrs

Genotypic-Phenotypic Correlation in ATTR



“Neurologic” **Phenotype** “Cardiac”

Genotypic-Phenotypic Correlation in ATTR



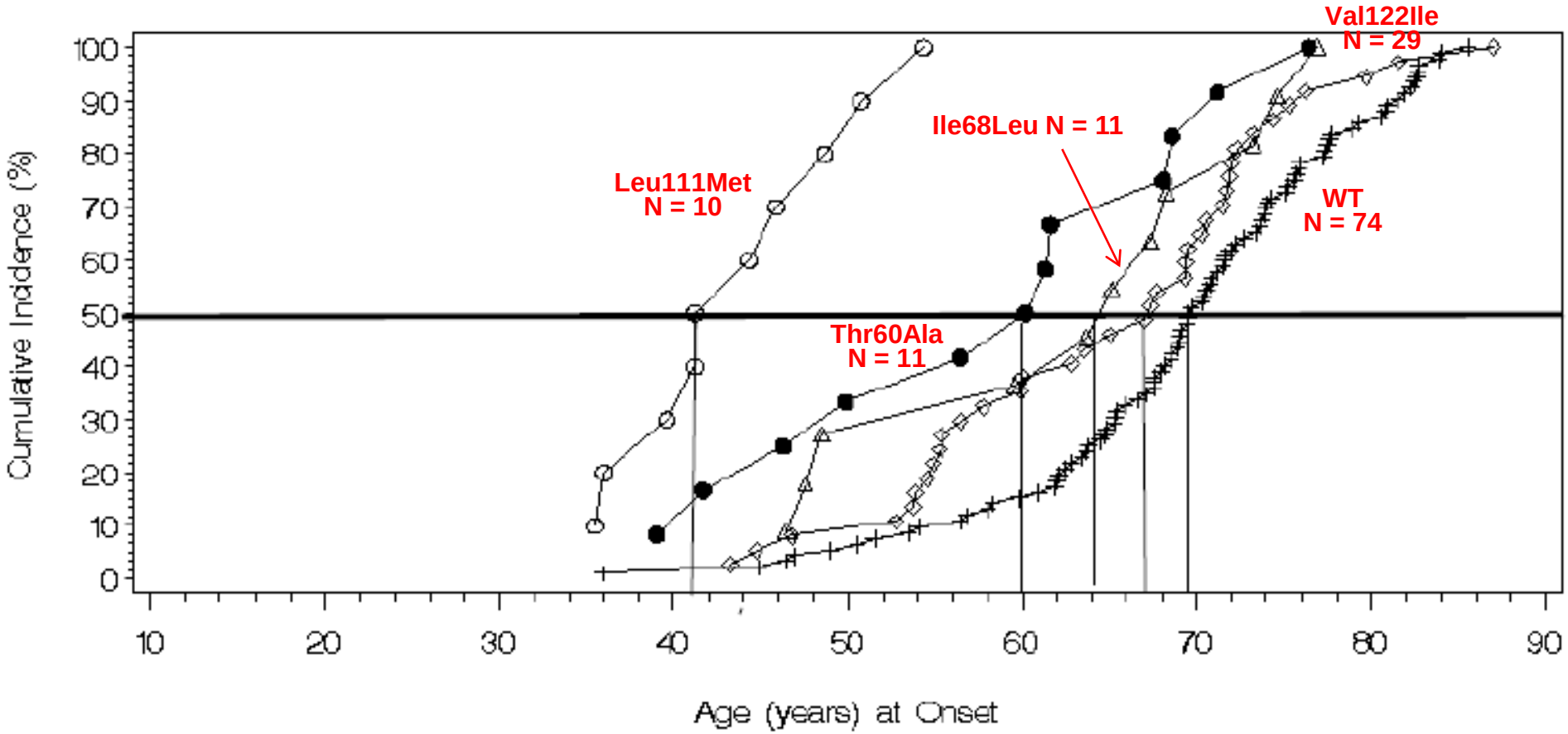
Clinical Characteristics of wt ATTR

Characteristic	Wild Type (N = 85)
Age at THAOS entry (yrs)	75.7
Males (%)	98.8
Caucasian (%)	88.2
African Descent (%)	3.5
Age at Onset (yrs)	71.0
Duration of symptoms (yrs)	3.3
NYHA class III-IV (%)	35
Atrial fibrillation (%)	63.3

Demographics and Baseline Characteristics of mATTR pts with «cardiac mutations»

Characteristic	Val122Ile (N = 39)	Ile68Leu (N = 15)	Thr60Ala (N = 15)	Leu111Met (N = 17)
Age at THAOS entry (yrs)	72.5	69.5	60.8	47.6
Males (%)	76.9	73.3	45.5	58.8
Caucasian	0.0	100.0	93.3	100.0
African Descent	87.2	0.0	0.0	0.0
Age at Onset (yrs)	69.4	66.2	61.4	42.8
Duration of symptoms (yrs)	2.3	3.9	4.8	4.3
NYHA Class III-IV (%)	53.8	26.7	26.7	23.5
Atrial fibrillation (%)	25.0	100.0	25.0	-

Onset of Disease in Patients with Cardiac Mutations or Wild Type TTR Amyloidosis



Baseline Echocardiographic findings of wt ATTR

Parameter	Wild Type (N = 85)
2D Echo structure	
LVIDd (mm)	44.3 (6.3)
IVS (mm)	18.2 (3.5)
PWT (mm)	16.8 (3.5)
LA size (mm)	51.4 (48.4)
Mitral Doppler	
E/A ratio	2.1 (1.4)
RVSP (mmHg)	37.2 (14.3)
Tissue Doppler	
E' septal (cm/sec)	4.7 (2.1)
LVEF (%)	45.5 (12.1)

Baseline Echocardiographic findings of mutant ATTR with cardiac phenotype

Parameter	Val122Ile	Ile68Leu	Thr60Ala	Leu111Met
2D Echo structure				
LVIDd (mm)	40.4 (7.4)	45.3 (3.7)	46.6 (3.3)	44.7(3.7)
IVS (mm)	18.4 (5.3)	16.3 (5.8)	16.3 (6.1)	13.3(4.1)
PWT (mm)	16.9 (4.1)	15.5 (4.7)	13.3 (4.7)	14.3(3.8)
LA size (mm)	42.1 (12.1)	45.5 (10.1)	41.8 (7.8)	40.8(5.5)
Mitral Doppler				
E/A ratio	3.1 (0.2)	2.0 (1.2)	-	-
RVSP (mmHg)	40.2 (4.7)	35	36	-
Tissue Doppler				
E' septal (cm/sec)	48.5	-	78.0	-
EF (%)	38.1 (15.6)	56.3 (10.37)	46.7 (11.69)	60.0(11.73)

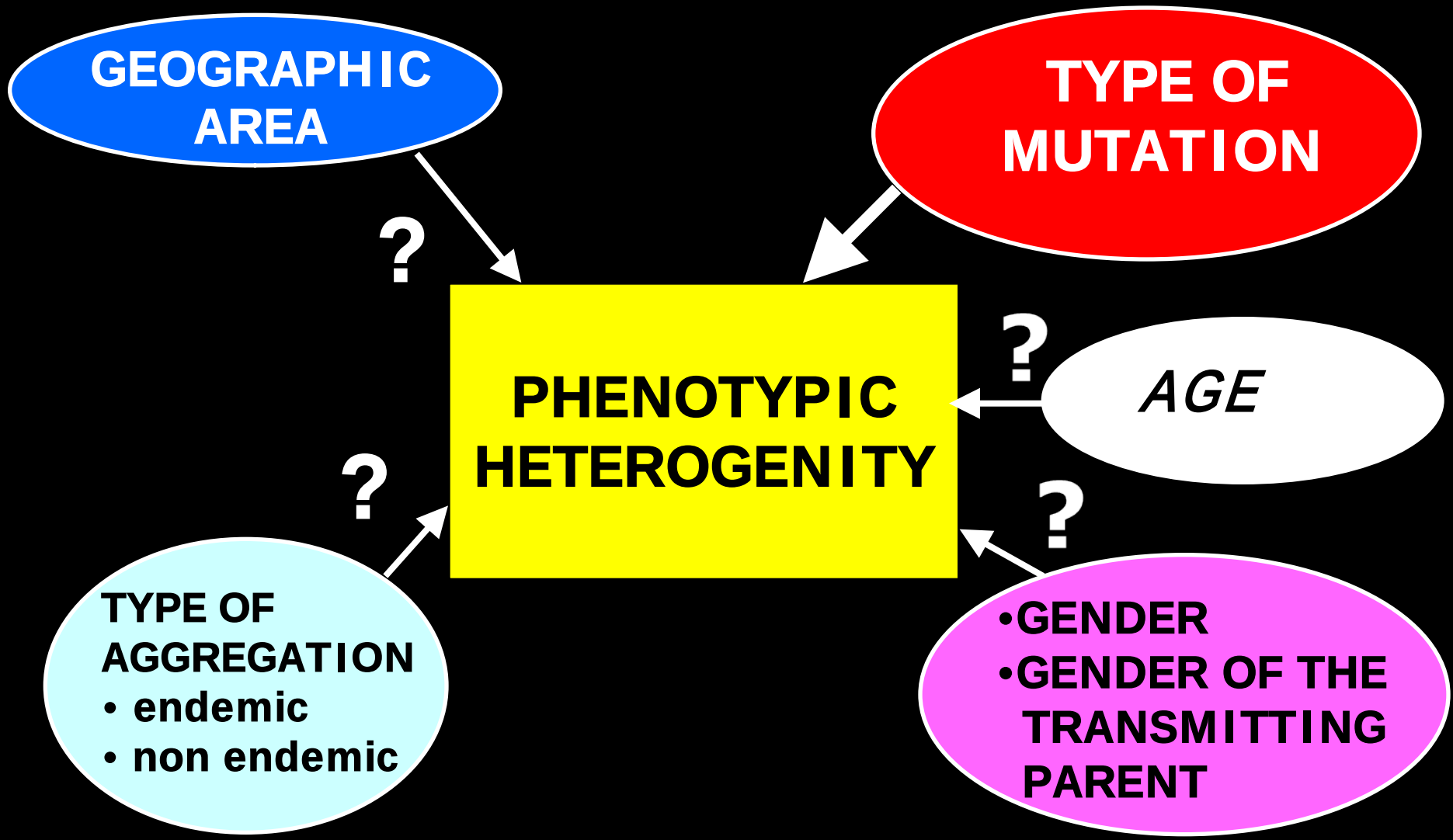
General Profile of ATTR patients with Exclusively Cardiac Phenotype

- Male gender
- Average age ~ 65 yrs
- No family history of ATTR
- Heart failure symptoms
- Concentric “LV hypertrophy”
- Absent or mild LV dilatation
- Mild LV systolic dysfunction
- (Normal or near normal QRS voltages)

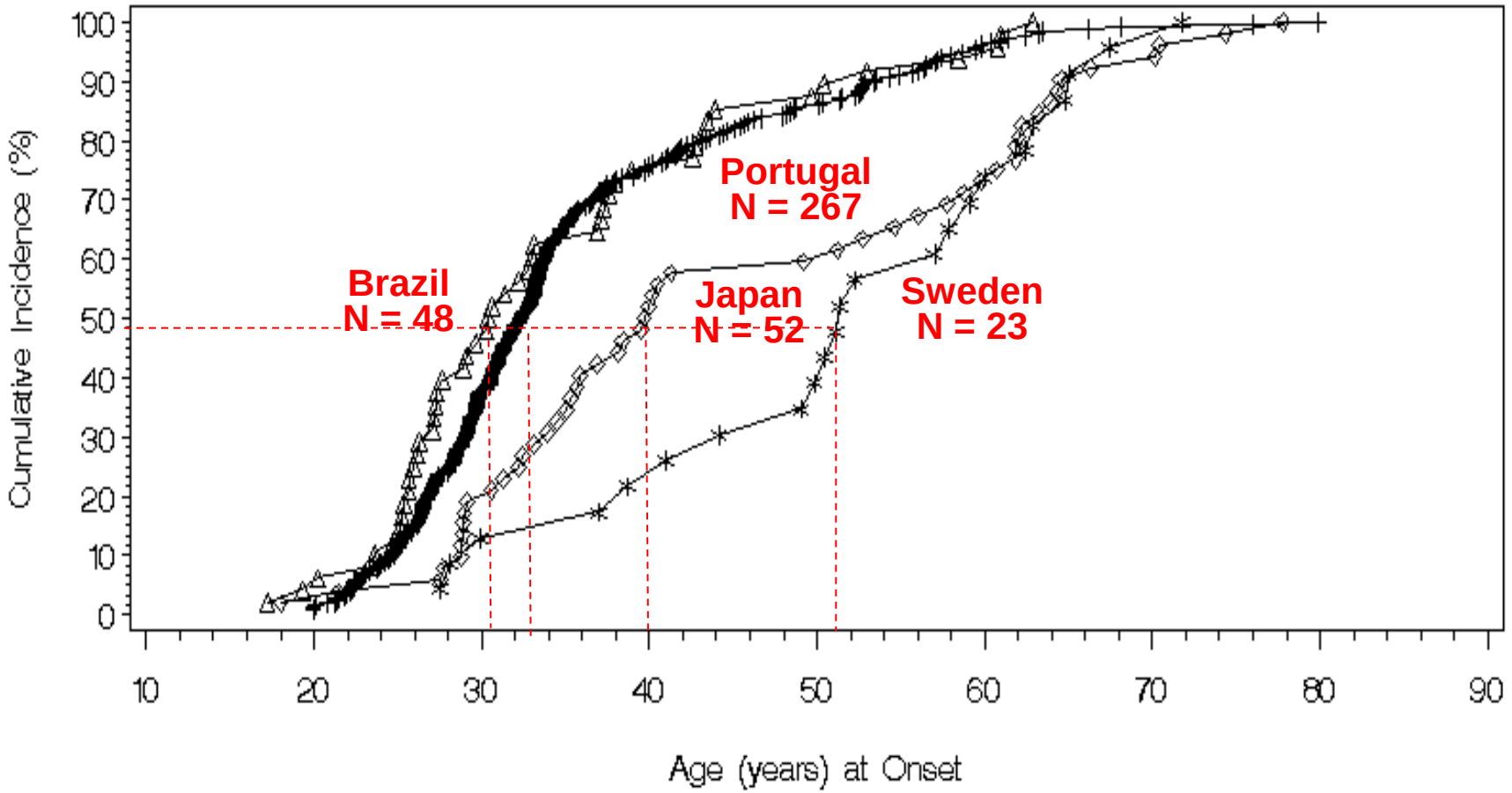
Cardiac involvement in V30M

Frequent but usually restricted to conduction disturbances. Cardiomyopathy rare (age-dependent). No isolated myocardial involvement. Symptomatic CMPs relatively frequent among late onset pts in nonendemic areas

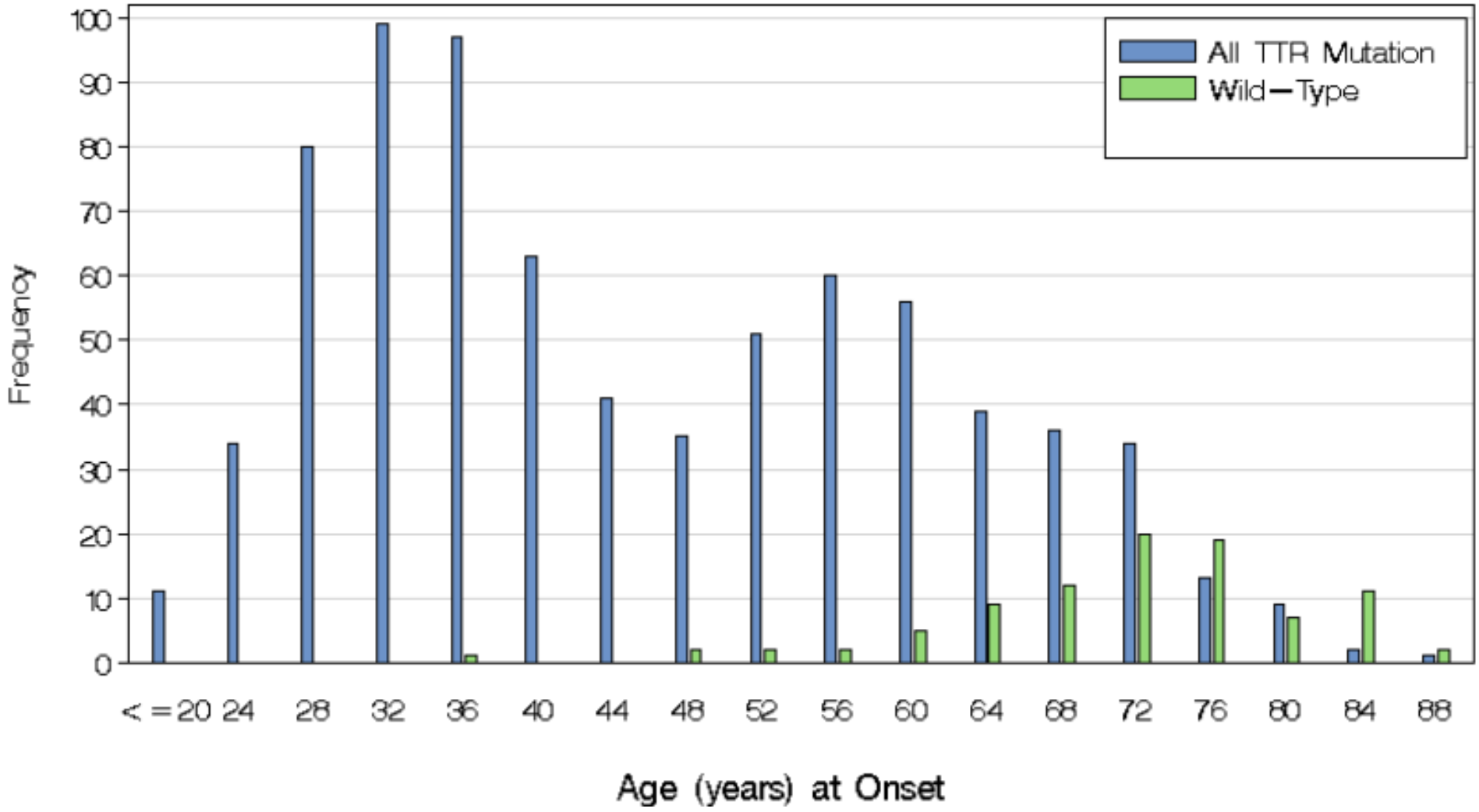
Main Determinants of Phenotypic Heterogeneity in ATTR



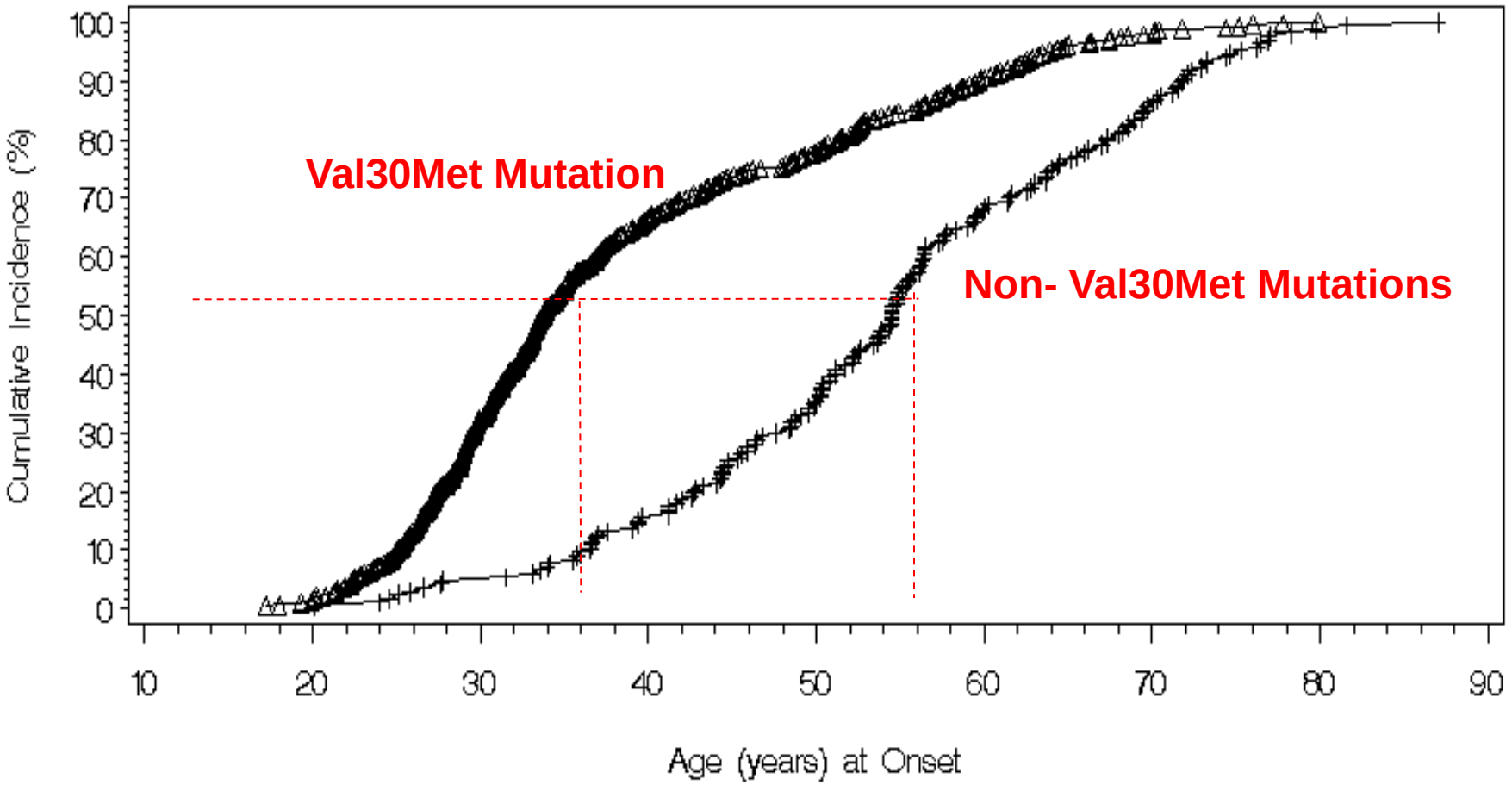
Onset of Disease in Patients with Val30Met Mutation- Geographic variation



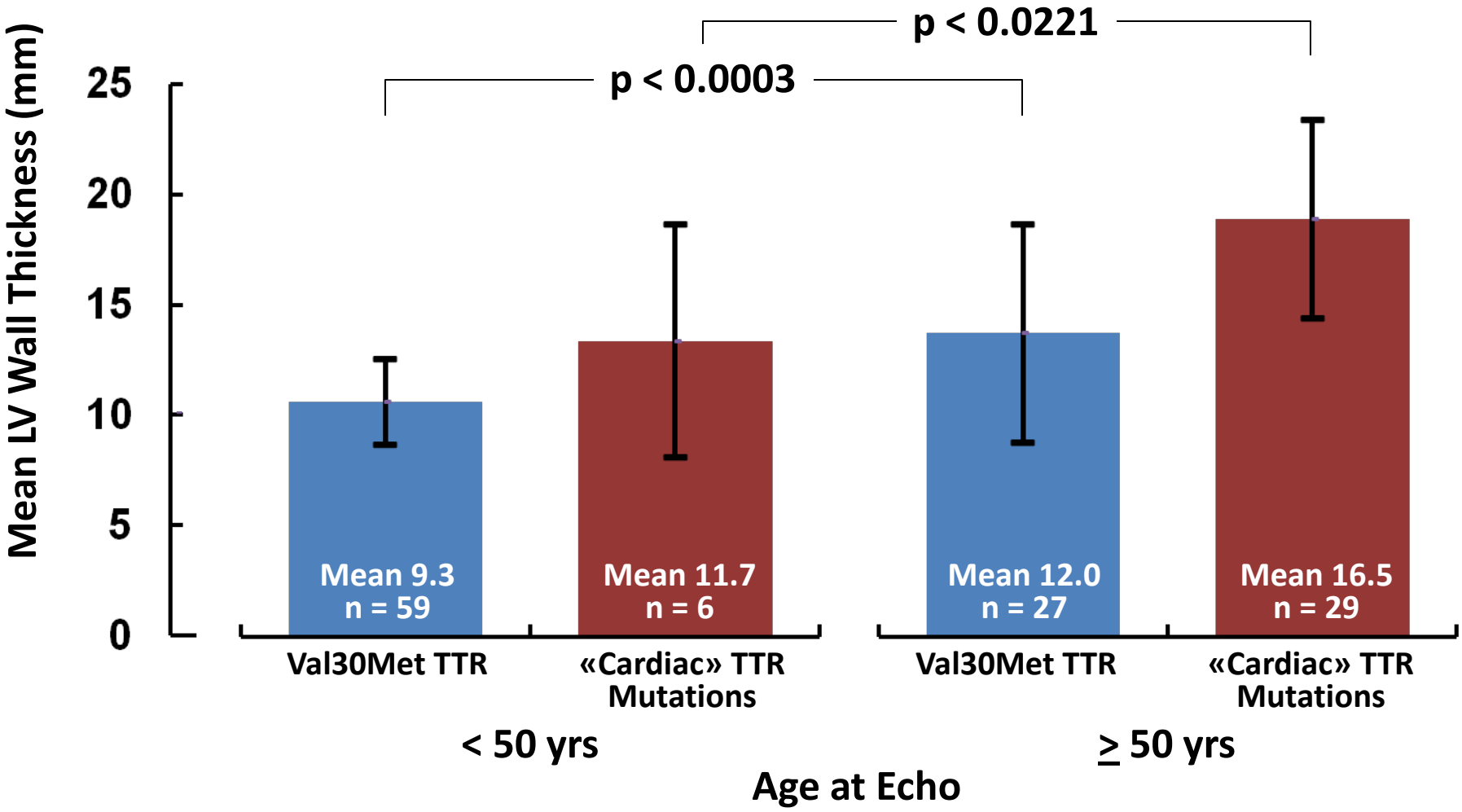
Age of Onset of Symptomatic Patients: TTRm & TTRwt



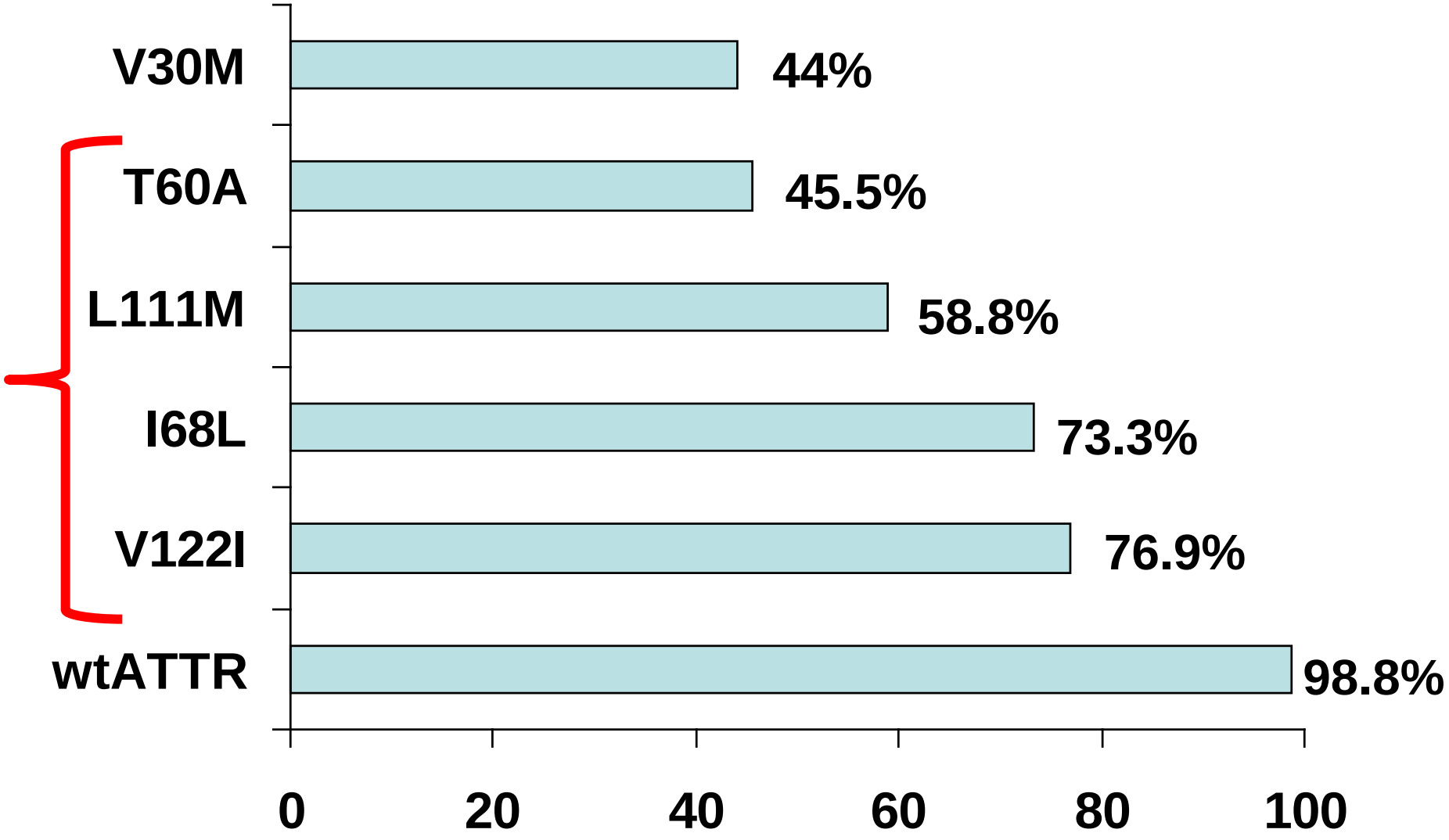
Cumulative Onset of Symptomatic Disease Patients with Val30Met and Non-Val30Met Mutations



LV Wall Thickness by Age



Male Prevalence in V30M, «Cardiac Mutations» and wtATTR



Multivariate Regression Analysis * (parameter estimate and p values)

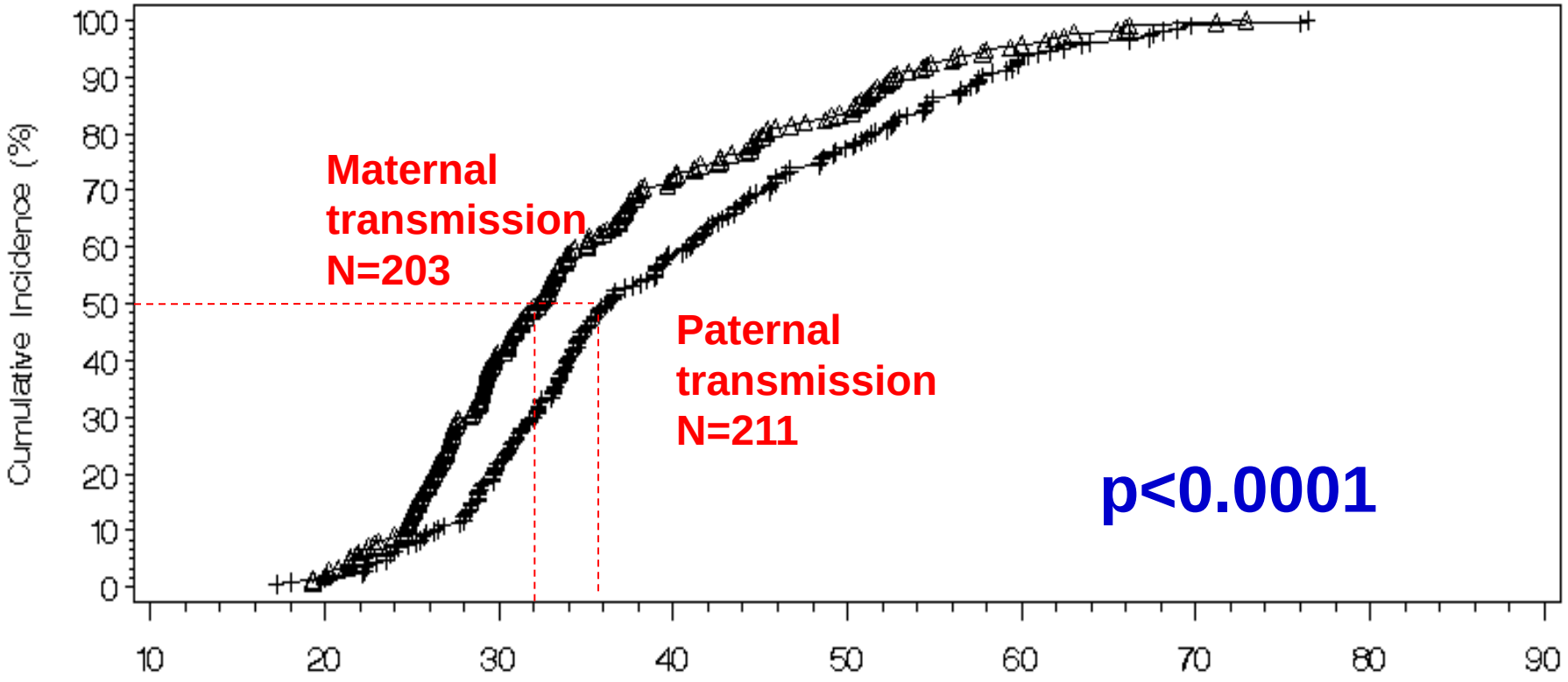
Variable	All patients	Cardiac mutations	V30M
Male gender	0.0082 (p=0.023)	0.0042 (p=0.65)	0.0044 (p=0.187)
Age at ECHO	0.0087 (p<0.0001)	0.0141 (p=0.0011)	0.0064 (p<0.0001)

***data from 227 pts with complete echocardiographic evaluation**

male gender and age = positive independent predictors of increasing mean parietal LV thickness in the overall population (age also among cardiac mutations and V30M)

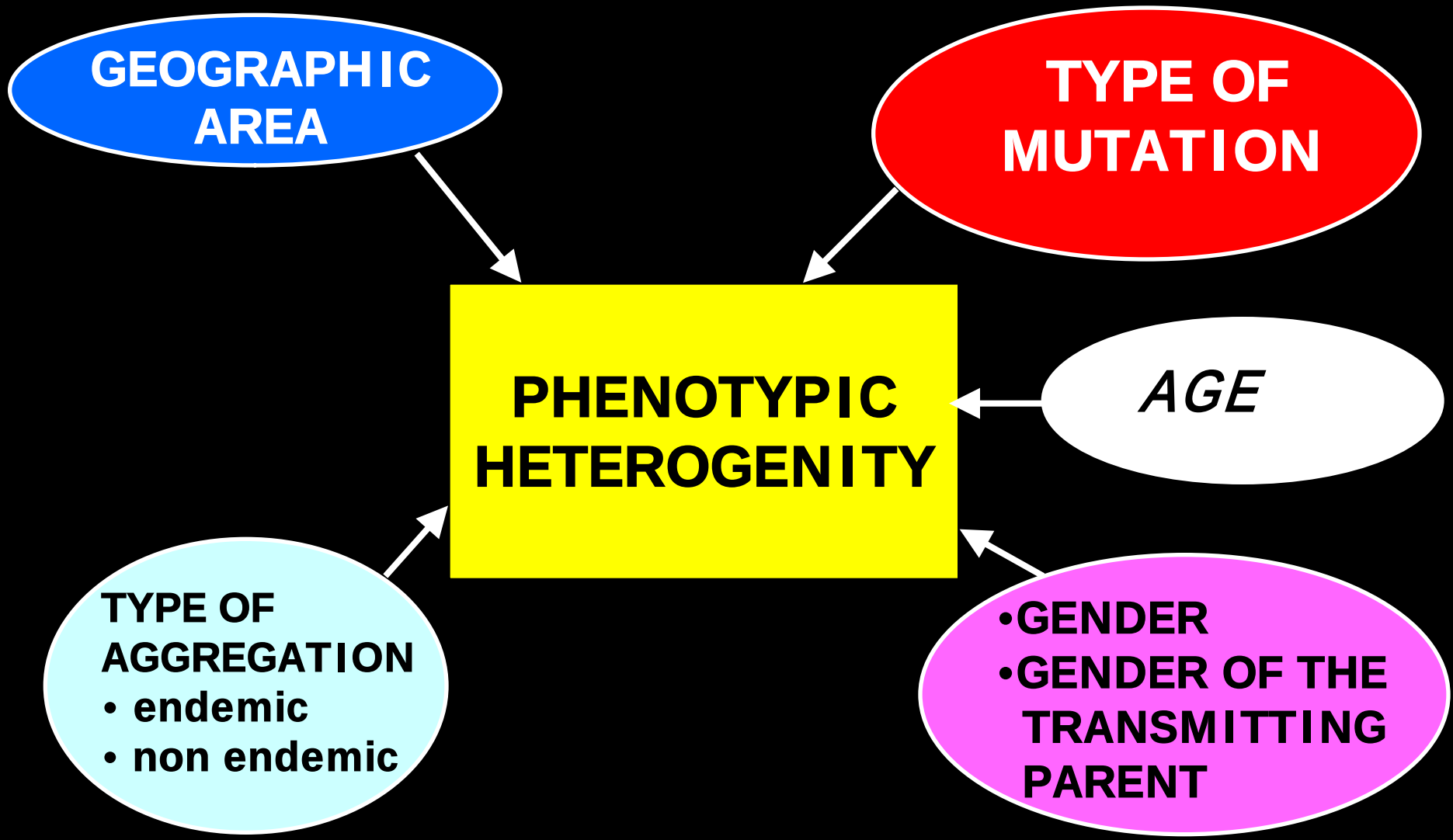
Onset of Disease

Dependence of Parental Inheritance



Earlier onset of ATTR amyloidosis with maternal transmission

Main Determinants of Phenotypic Heterogeneity in ATTR



Conclusions:

- ✓ **THAOS registry offers a unique opportunity to assess the worldwide phenotypic and genotypic spectrum and correlations in ATTR.**
- ✓ **Both genotype and phenotype are highly heterogeneous.**
- ✓ **Phenotypic heterogeneity is not only linked to genotype, but also to geographic distribution, age, gender of the patient and of the transmitting parent.**
- ✓ **Myocardial involvement is less pronounced in women, supporting the hypothesis that some biologic characteristic may protect women against myocardial TTR-related amyloid infiltration**

Conclusions:

- ✓ A clinically relevant subset of mutant Caucasian and African-American patients (around 10%, mainly associated with four different mutations) and all wt-ATTR have a dominant cardiac phenotype at presentation mimicking HCM
- ✓ Symmetric LVH and mildly depressed LVEF especially in elderly men should prompt the suspicion of ATTR among patients with apparently unexplained LVH.
- ✓ THAOS registry will hopefully gain insight into the natural history of the disease and offer the opportunity to evaluate novel therapeutic modalities