UNIVERSITÀ DEGLI STUDI FIRENZE

Azienda Ospedaliero Universitaria Careggi

LA POLINEUROPATIA HATTR: VERSO UN PROTOCOLLO DIAGNOSTICO REGIONALE –INSTANT FAP-Network

I dati epidemiologici

Dr. Michele Vastola

AMILOIDOSIfirenze

Centro Fiorentino per la diagnosi e la cura delle Amiloidosi

SNO CIENZE EUROLOGICHE SPEDALIERE

Sin SOCIETÀ ITALIANA DI NEUROLOGIA

What is the prevalence of ATTRm in the world?

ESTIMATING THE GLOBAL PREVALENCE OF TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

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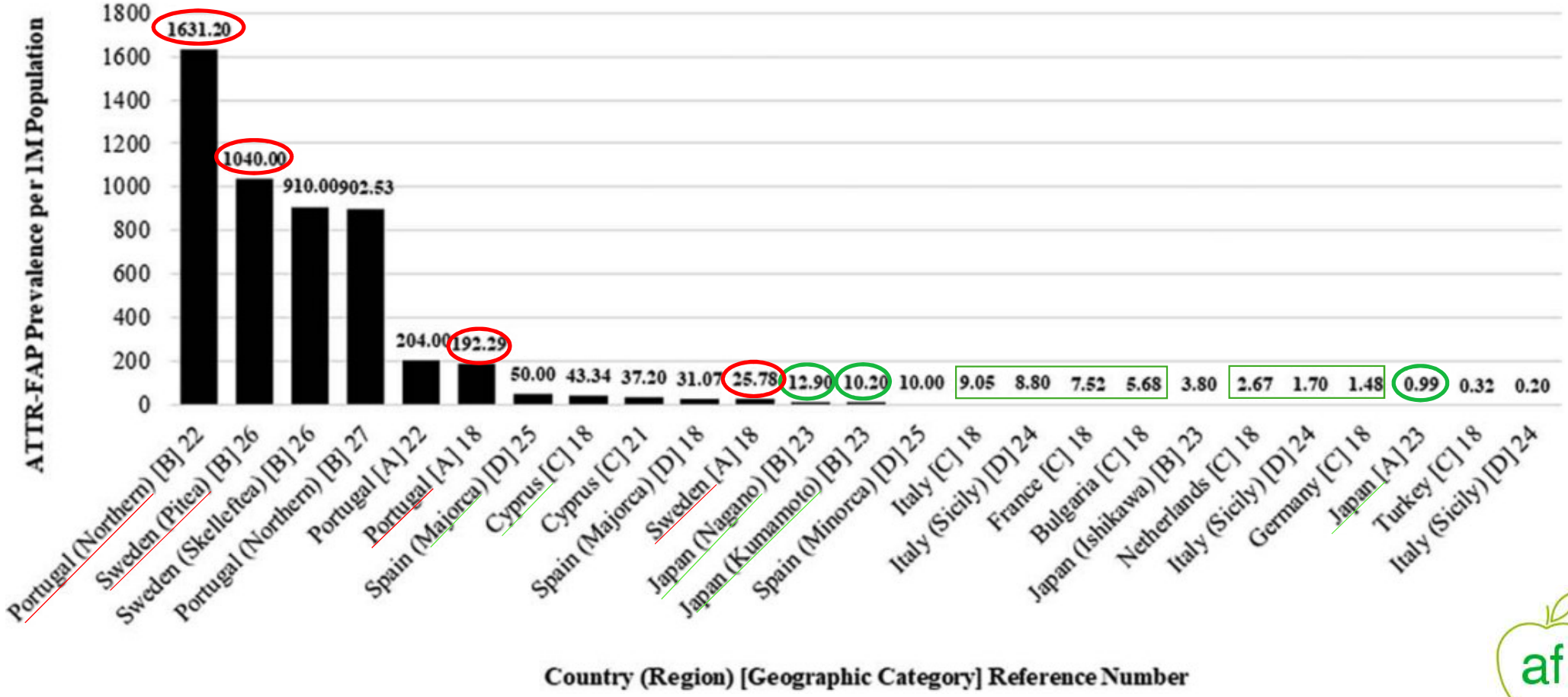


FA1

FA5

FA8

FA7

The cumulative estimated number of persons with ATTR-FAP was:

Country	General population, M	Prevalence low	Prevalence mid	Prevalence high
Core (10 countries)	460.1	3,639	3,762	3884
Turkey	78.7	25	25	25
Bulgaria	7.2	41	41	41
Netherlands	16.9	45	45	45
Cyprus	1.2	51	51	51
Germany	81.4	121	121	121
Japan	127.0	111	123	135
Sweden	9.8	253	253	253
France	66.8	502	502	502
Italy	60.8	500	550	600
Portugal	10.3	1,990	2,051	2111
Extrapolated (32 countries)	4,122.2	1,887	6,424	3,4584
Luxembourg	0.6	0	1	4
Slovenia	2.1	1	3	16
Ireland (North)	1.9	1	3	14
New Zealand	4.6	1	7	35
Finland	5.5	2	8	41
Denmark	5.7	2	8	43
Israel	8.4	3	12	63
Switzerland	8.3	3	12	62
Austria	8.6	3	13	65
Hungary	9.8	3	15	74
Czech Republic	10.6	3	16	79
Greece	10.8	3	16	81
Belgium	11.3	4	17	85
Ecuador	16.1	5	24	121
Romania	19.8	6	29	149
Sri Lanka	21.0	7	31	158
Taiwan	23.5	8	35	177
Australia	23.8	8	35	179
Korea (South)	50.6	16	75	381
Malaysia	30.3	10	45	228
Canada	35.9	12	53	270
Poland	38.0	12	56	286
Argentina	43.4	14	64	326
Spain	46.4	15	69	349
UK	65.1	21	97	490
Mexico	127.0	41	188	955
Russia	144.1	46	214	1,084
Bangladesh	161.0	52	239	1,211
Brazil*	207.8	623	623	5,078
USA†	321.4	104	476	2,488
India	1,311.1	423	1,943	9,858
China	1,347.7	435	1,997	10,134

Diapositiva 4

FA1 For countries with reported prevalence estimates, the total number of persons with ATTR-FAP was calculated as the prevalence rate per million (1M) multiplied by the general population expressed in millions. When multiple prevalence rates were reported for a country, we first constructed a range consisting of a low prevalence estimate and a high prevalence estimate.
Federica Azzolini; 06/10/2020

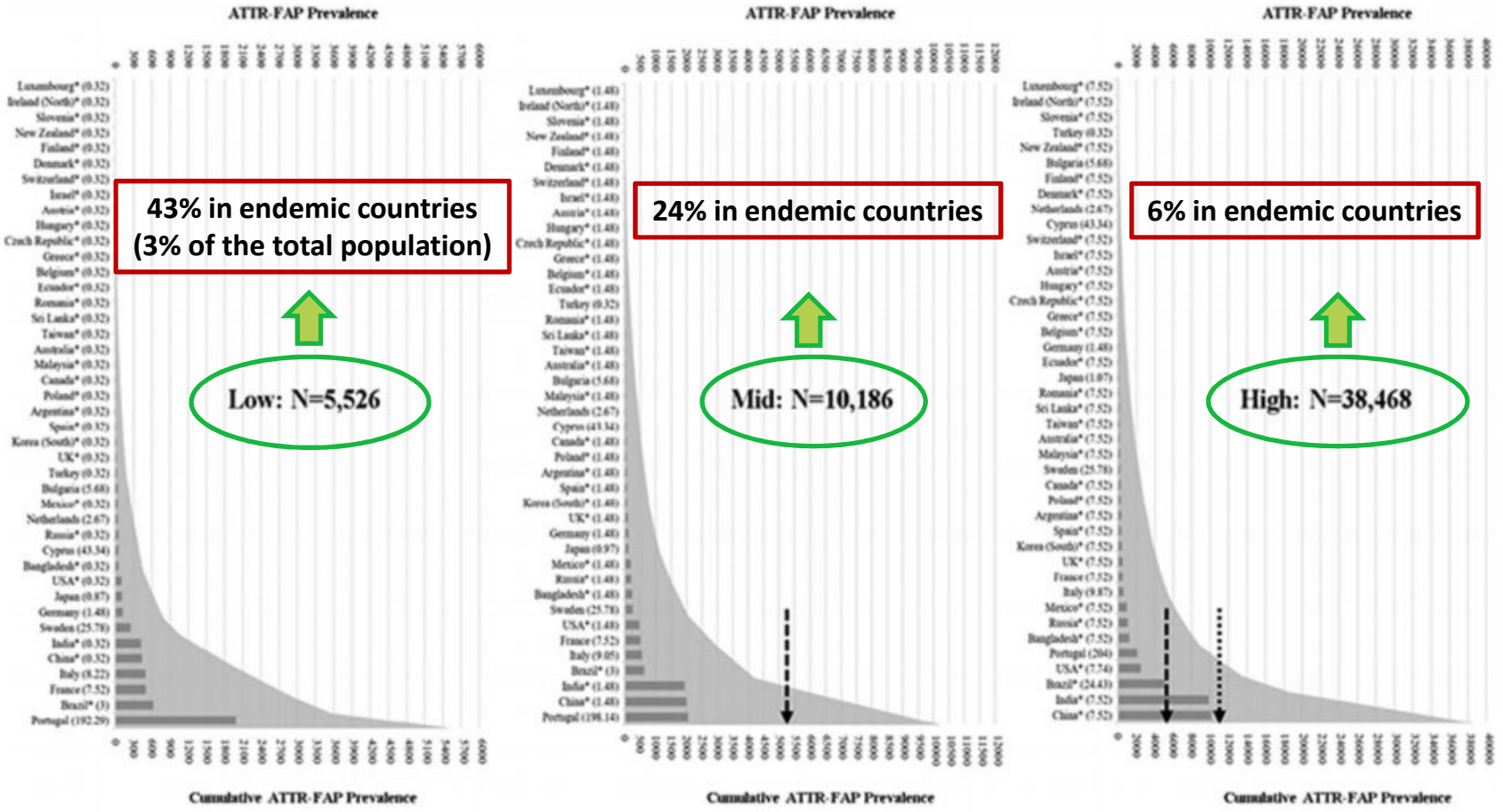
FA5 Extracted prevalence estimates were extrapolated to countries in which ATTR-FAP cases have been reported but prevalence has not. These countries were identified from (1) a recently presented case series of 532 ATTR-FAP cases published between 2005 and 2015, (2) a list of countries with at least 1 clinic site enrolling patients into the THAOS, and (3) countries that are known to the authors to have ATTR-FAP patients. Unless additional information was available, the low, mid, and high prevalence estimates for these extrapolated countries were calculated as the lowest, middle, and highest nonendemic national prevalence rates extracted from the literature multiplied by general population size.
Federica Azzolini; 07/10/2020

FA8 The low, mid, and high nonendemic national prevalence estimates applied to the extrapolated countries were 0.32/1M (Turkey), 1.48/1M (Germany), and 7.52/1M (France), respectively.
Federica Azzolini; 07/10/2020

FA9 For these extrapolated estimates, we applied the lowest prevalence rates to generate conservative values in the base case, and we explored realistic ranges by applying other appropriate prevalence multipliers. Mediating population-level factors were also considered. For example, in Brazil, the cumulative national prevalence was derived based on Portuguesedescended and non–Portuguese-descended subpopulations separately.
Federica Azzolini; 07/10/2020

FA7 ATTR-FAP population sizes reported for the extrapolated countries should be interpreted more cautiously because these estimates were subject to a greater degree of author judgment compared with core country estimates.
Federica Azzolini; 07/10/2020

Total "at risk" population from **42 countries**:
<u>4.6 billion persons</u> (60% of the global population)



Additional cases might be found in the remaining 40% of the global population, primarily in former Portuguese colonies…

Global estimated prevalence:

5,000 to 10,000 (but..... it might be as high as 38,000 persons)

Endemic in:

- Portugal
- Sweden

With foci in:

- Japan
- Brazil
- Maiorca
- Cyprus


What is the prevalence of ATTRm in Europe?
SPAIN
MADRID
Barcelona
Sierra Morena
Córdoba
Sevilla
Balearic Is.
Menorca
Mallorca
Marseille
Corsica
ITALY
ROME
Naples
Sardinia
Apennines
ALGIERS
Oran
Constantine
Annaba
Fes
Meknes
Atlas Mountains
TUNIS
TUNISIA
Palermo
Messina
Sicily
VALLETTA
Malta
Corfu
ALBANIA
TIRANA
AUSTRIA
HUNGARY
BUDAPEST
SLOVAKIA
BRATISLAVA
BOSNIA H.
YUGO SLAVIA
BELGRADE
SOFIA
ROMANIA
POLAND
WARSAW
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CURRENT OPINION

Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP

Table 1. National prevalence of transthyretin familial amyloid polyneuropathy across Europe

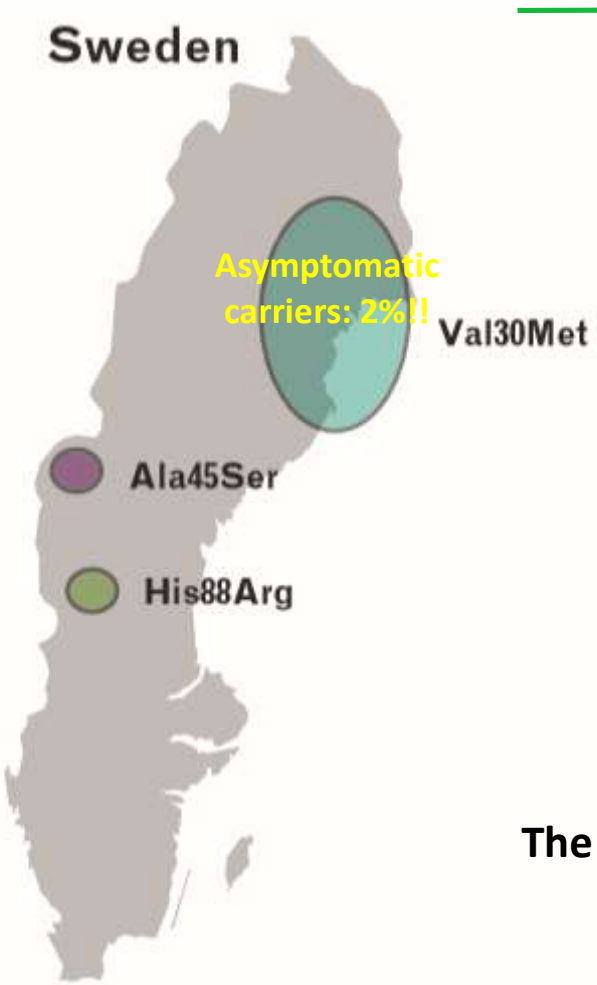
	Total population (millions) [36]	Surface area (thousands, km^2) [36]	Number of diagnosed, symptomatic TTR-FAP cases	Number of asymptomatic carriers of *TTR* gene mutation	Age range of patient cohort (years)
Portugal	10.4	92.2	2000	>500	18–87 (most <50)
Sweden	9.6	438.6	250	Estimated 7500 in clustering area in Northern Sweden from a population of 250 000	25–85
France	65.8	632.8	500	200	22–86
Italy	60.8	302.1	500–600	250	25–85
Spain/Majorca[a]	46.5	506.0	27	58	40–75
Bulgaria	7.3	110.0	41	14	44–63
Germany	80.5	357.3	120	60	28–69
Netherlands	16.8	41.5	45	23	25–75
Cyprus[a]	0.9	9.3	50	140	20–75
Turkey	75.0[b]	783.6[b]	20–30	16	21–66

Yesim Parman[a], David Adams[b], Laura Obici[c], Lucía Galán[d], Velina Guergueltcheva[e], Ole B. Suhr[f], Teresa Coelho[g], from the European Network for TTR-FAP (ATTReuNET)

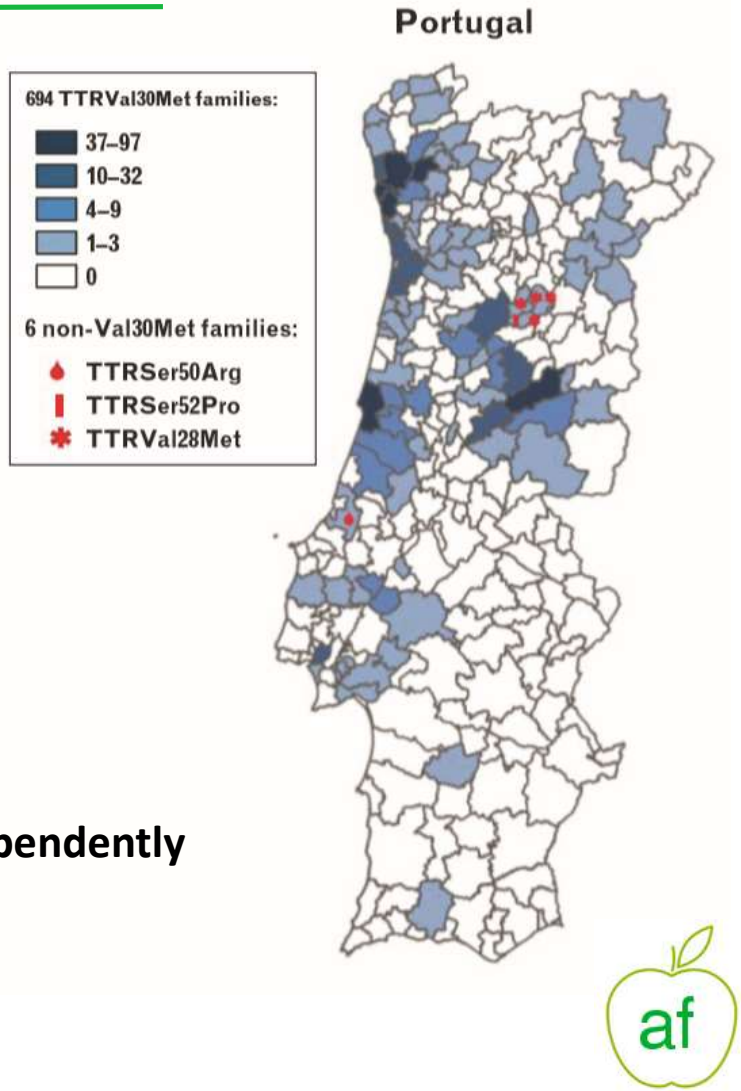
Diapositiva 8

FA10 These estimates were based on a survey of European ATTR-FAP clinicians and researchers that reported their impressions, but not necessarily direct observations, of ATTR-FAP prevalence in their respective countries.
Thus, the prevalence rates reported in Parman et al. were generated from the responses of 15 ATTR-FAP clinical and epidemiological experts practicing in Europe.
Federica Azzolini; 07/10/2020

Endemic countries



In some areas prevalence ranges from 1/1,000 to 1/10,000 persons.

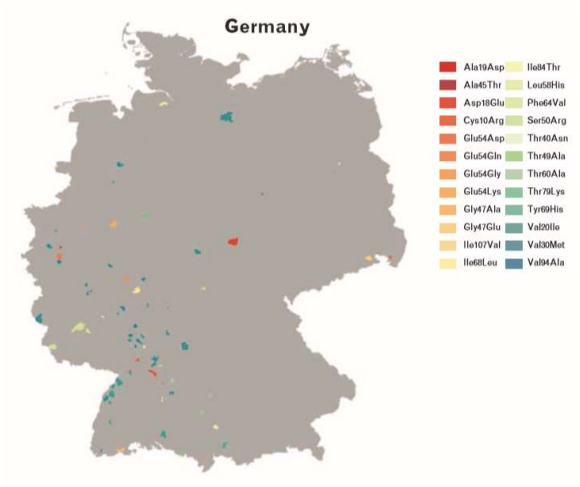


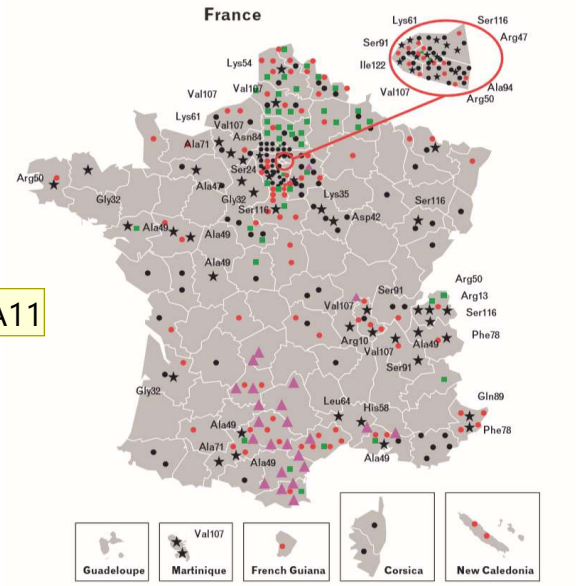
Genetic homogeneity:

- 95% V30M in Sweden
- 99% V30M in Portugal

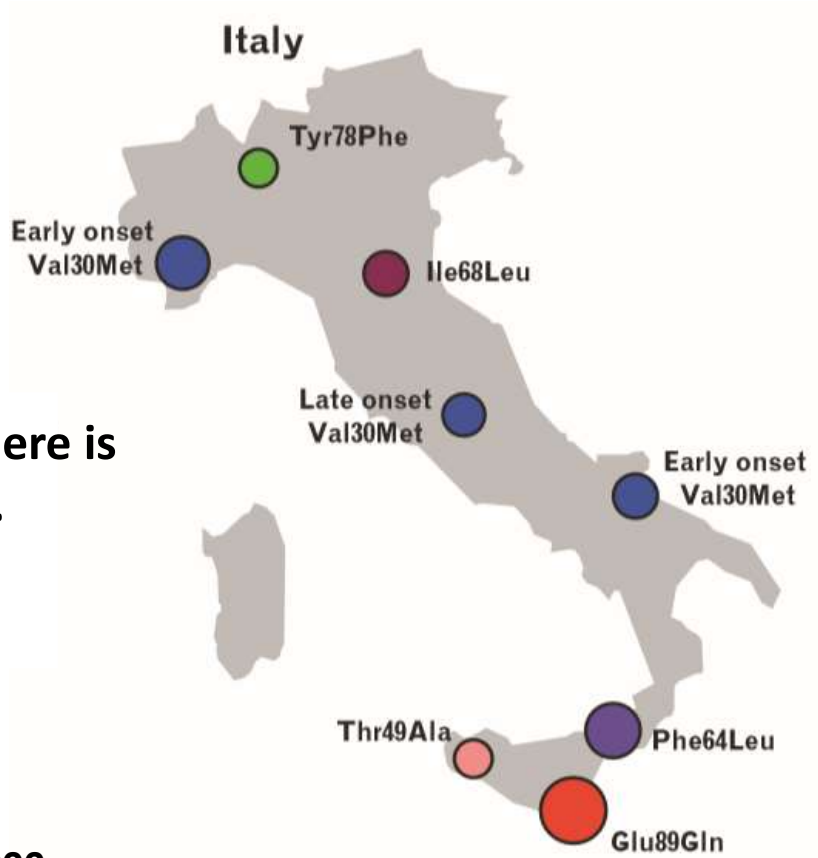
The mutations is belived to have arisen independently in Portugal and Sweden

Non-Endemic countries





FA11



In nonendemic countries there is genetic heterogeneity.

Prevalence: 0.2-9.05/1,000,000

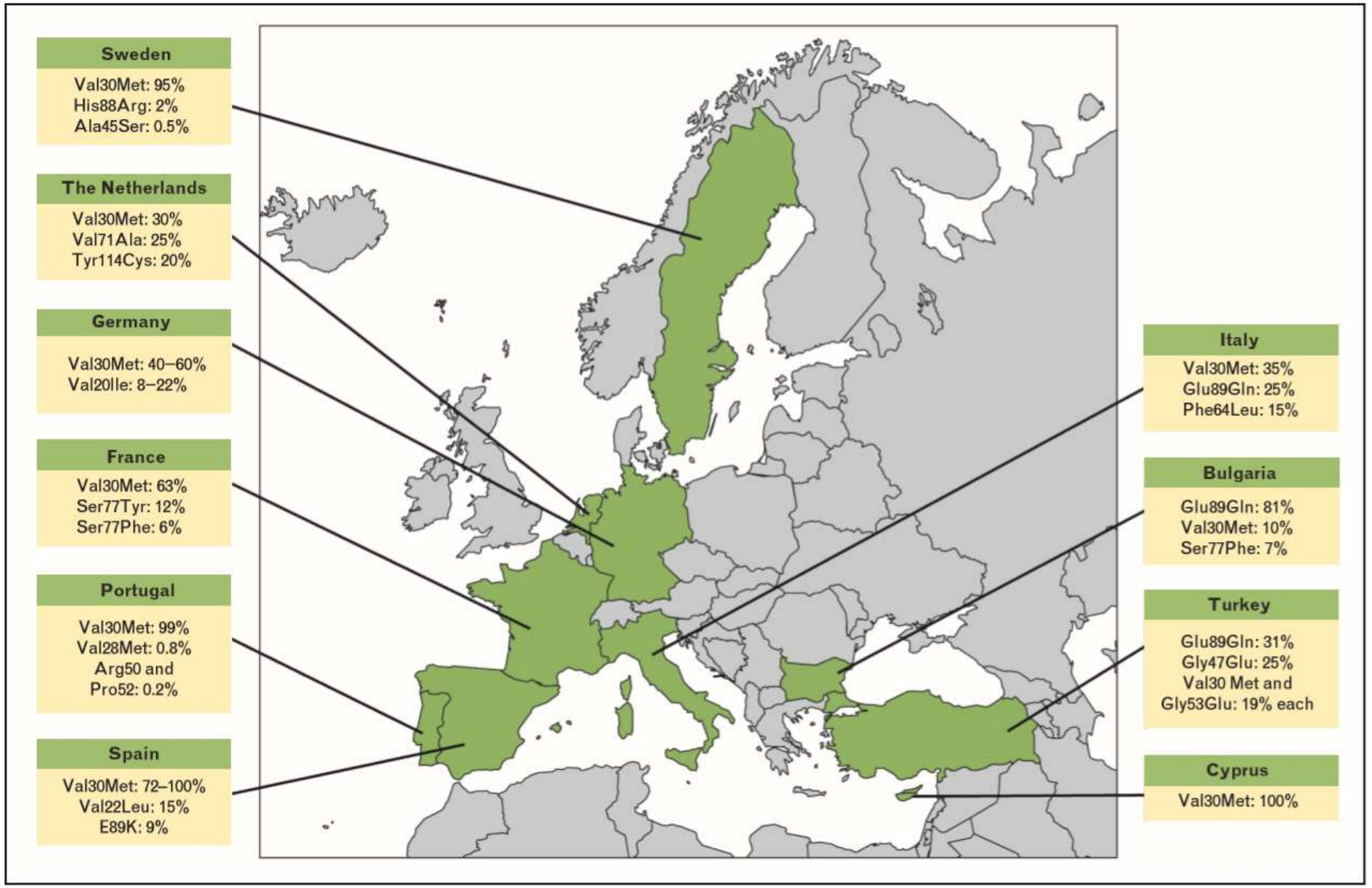
TTR Met30 Port (full black circles); TTR Met30 non Port (full red circles); TTR Tyr77 (green full square); TTR Phe77 (pink full triangles); stars: non Met30 TTR-FAP (neither Tyr77, nor Phe77; in details).

Diapositiva 10

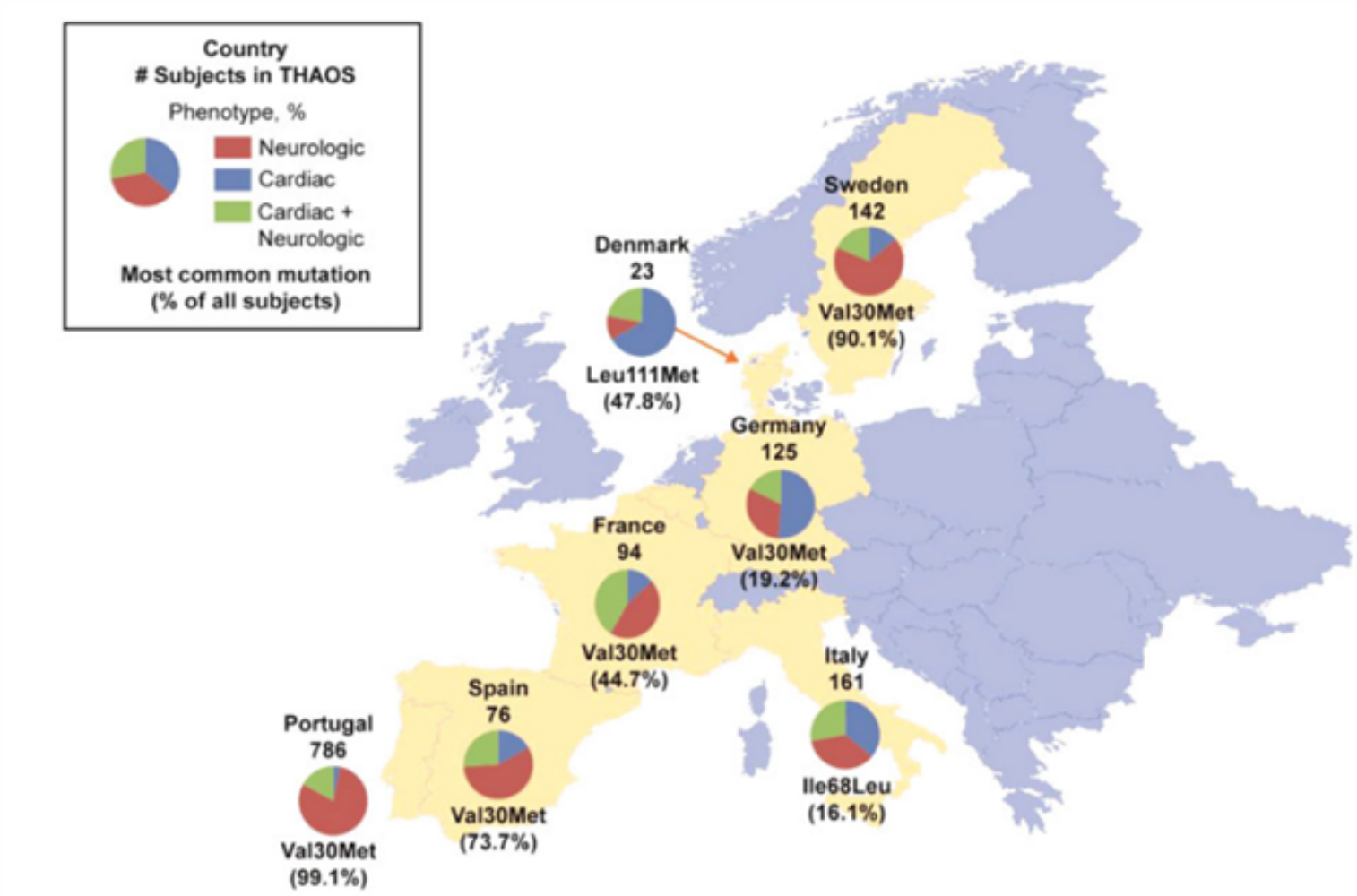
FA11 In France more than 29 mutations have been identified. Val30Met is the most common (62% of cases). This may relate to a large immigration from Portugal to France in the early 1970s.
Tyr77Ser (11.8%) and Phe77Ser (6.2%).
Federica Azzolini; 07/10/2020

Genetics

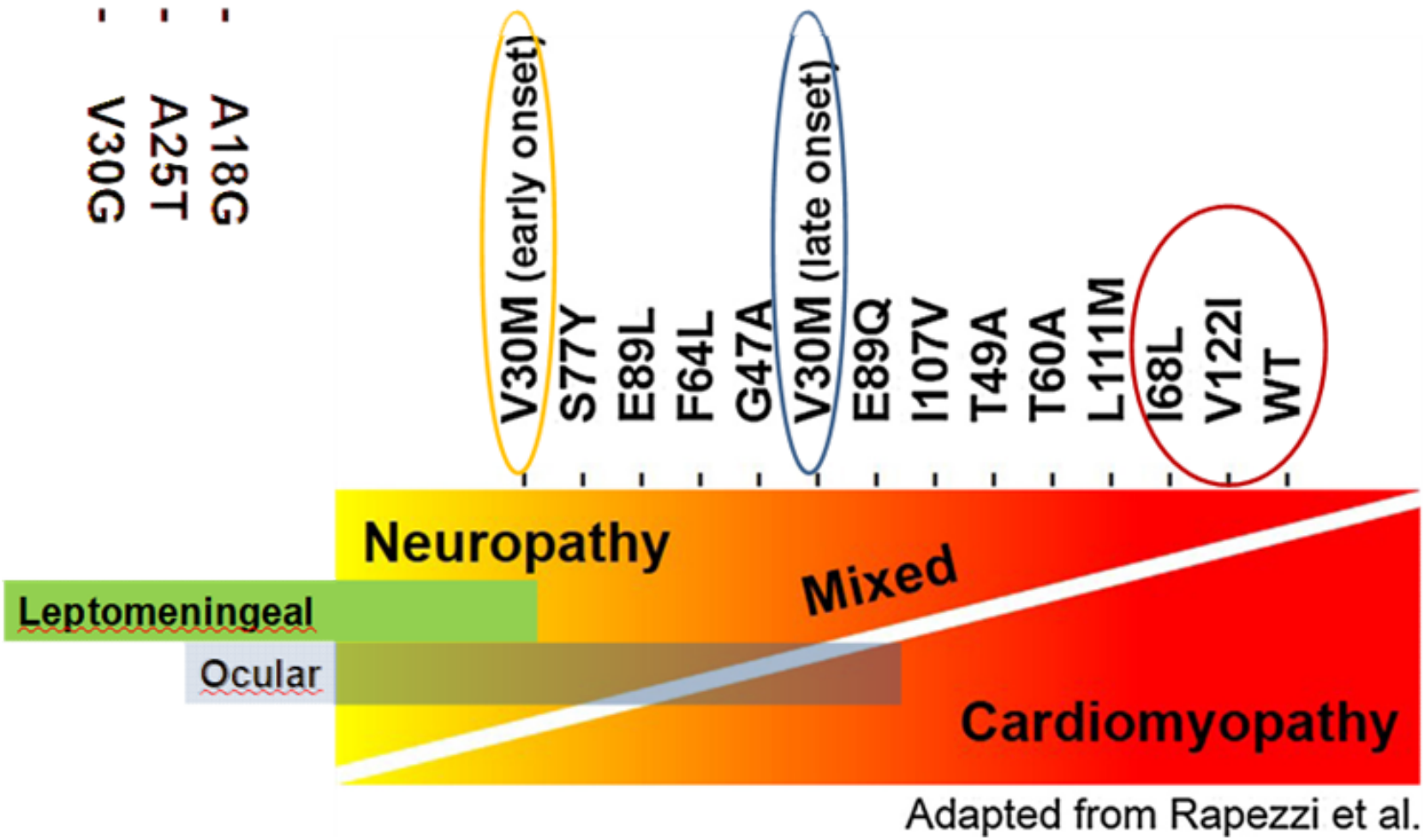
- More than 100 different mutations identified.
- ~ 50-70% of patients worldwide carry the V30M mutation.
- Also in Europe Val30Met is the most common mutation, but there is heterogeneity around the second-most prevalent mutation.


Sweden
Val30Met: 95%
His88Arg: 2%
Ala45Ser: 0.5%
The Netherlands
Val30Met: 30%
Val71Ala: 25%
Tyr114Cys: 20%
Germany
Val30Met: 40–60%
Val20Ile: 8–22%
France
Val30Met: 63%
Ser77Tyr: 12%
Ser77Phe: 6%
Portugal
Val30Met: 99%
Val28Met: 0.8%
Arg50 and
Pro52: 0.2%
Spain
Val30Met: 72–100%
Val22Leu: 15%
E89K: 9%
Italy
Val30Met: 35%
Glu89Gln: 25%
Phe64Leu: 15%
Bulgaria
Glu89Gln: 81%
Val30Met: 10%
Ser77Phe: 7%
Turkey
Glu89Gln: 31%
Gly47Glu: 25%
Val30 Met and
Gly53Glu: 19% each
Cyprus
Val30Met: 100%

Genotype-Phenotype correlation



Genotype-Phenotype correlation

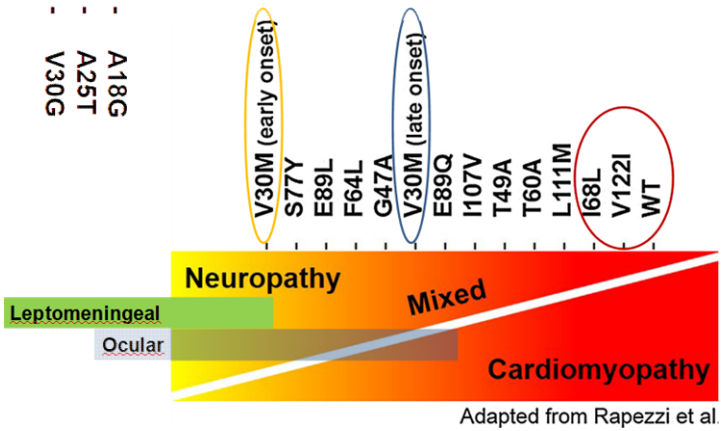


Adapted from Rapezzi et al.

Val30Met

Early onset (Portugal, Cyprus, and Majorca)

- The average age of onset in Portugal is 33.5 yy
- High penetrance in Portugal (80% at 50 yy)
- Women have a later onset than men (33.7 vs 29.0 yy)



Adapted from Rapezzi et al.

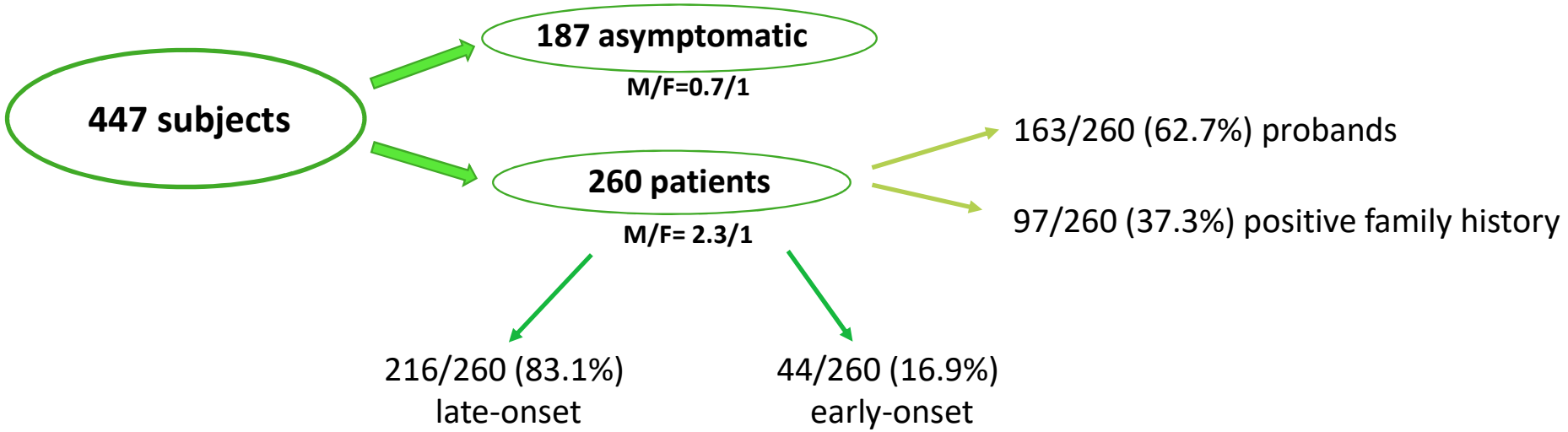
Late onset (Sweden, and nonendemic areas)

- The average age of onset in Sweden is 56-57 yy
- Low penetrance in Sweden (1.7% at 30 yy, 69% at 90 yy)
- A male predominance has been observed
- Cardiomyopathy is predominant in late-onset male patients
- Higher penetrace and earlier onset when the mutation is inherited from the mother rather than from the father

What about Italy?

Italy: the Italian Registry

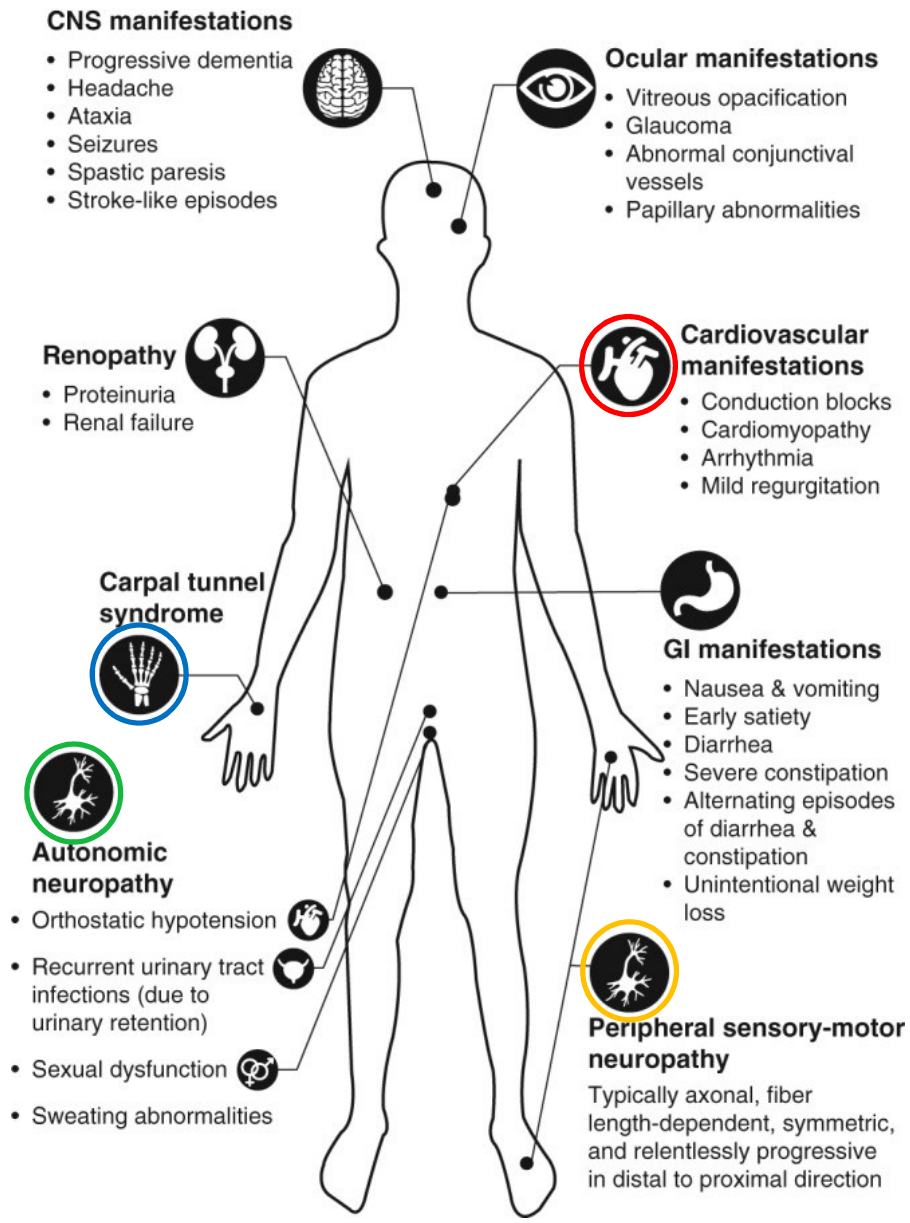
Global prevalence: 4.33/million (9.2-9.3/million in Calabria and Sicily)



The Italian prevalence might be even higher:

- participation to the Registry on a volunteer basis
- paucisymptomatic relatives of patients may escape medical attention
- some Italian regions have no referral centres (eg. Sardinia island have no ATTRm patient so far diagnosed)

ATTRv amyloidosis Italian Registry: clinical and epidemiological data Amyloid. 2020 Jul 22;1-7.



Cardiomyopathy: 67/260 (**25.8%**)

Neuropathy: 124/260 (**47.7%**)

Dysautonomia: 9/260 (**3.5%**)

CTS: 21/260 (**8.1%**)

Mixed phenotype: 39/260 (**15%**)

The average **diagnostic delay** was **2.58 yy**
(3.4 yy in probands, 1.2 yy in patients with positive family history)

48/163 (**29.4%**) probands received a **misdiagnosis**
(25/48 CIDP)

Italy: the Italian Registry

31 different mutations recorded

In patients (260):

- **V30M** was the 1st most frequent mutation (60/260; 23.1%)
- 48/60 (80%) V30M was late-onset
- 20/60 (20%) V30M was early-onset
- **F64L** was the 2nd most frequent mutation (58/260; 22.3%)
- **I68L** was the 3rd most frequent mutation (47/260; 18.1%)

In all subjects (447):

- **I68L** was the 1st most frequent mutation (100/447; 22.4%)
- **F64L** was the 2nd most frequent mutation (91/447; 20.4%)
- **V30M** was the 3rd most frequent mutation (90/447; 20.1%)

Italy: the Italian Registry

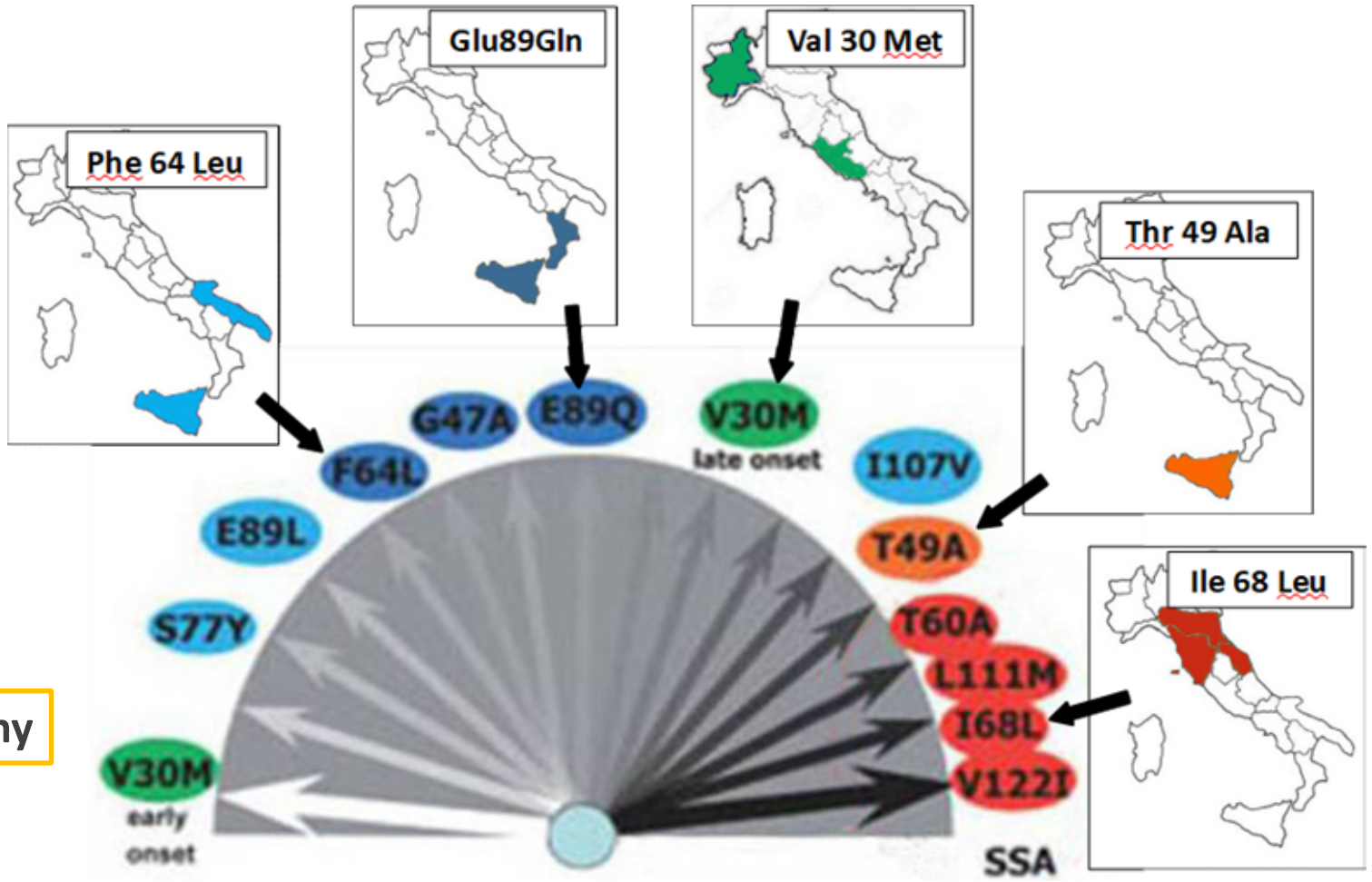
Considering the 7 most common variants:

- **V30M**, **I68L**, **F64L** and **V122I** are not restricted to a unique geographic area

  → ancient origin? different foci?

- **T49A**, **E89Q** and **Y78F** seem to have a clear common ancestry, respectively, from Agrigento, Syracuse and Bergamo

Genotype-Phenotype correlation



Neuropathy

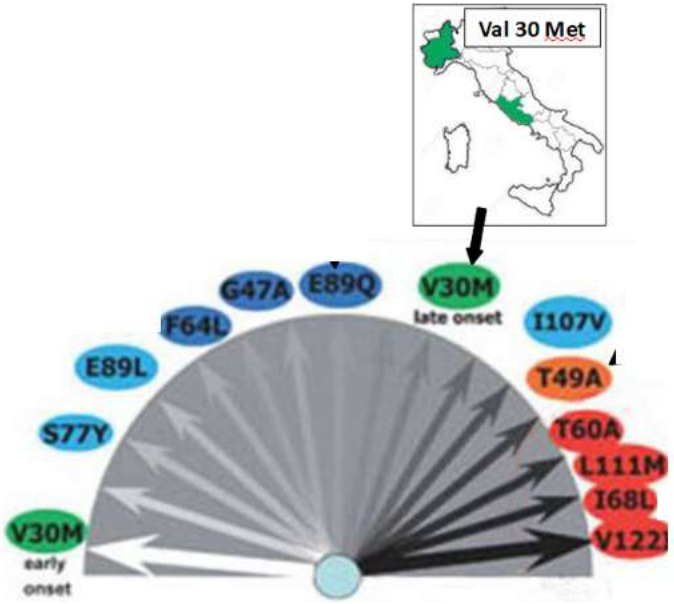
Cardiopathy

af

V30M in Italy

An independent origin of the V30M mutation has been postulated comparing Italian haplotypes with those from Portuguese and Swedish patients.

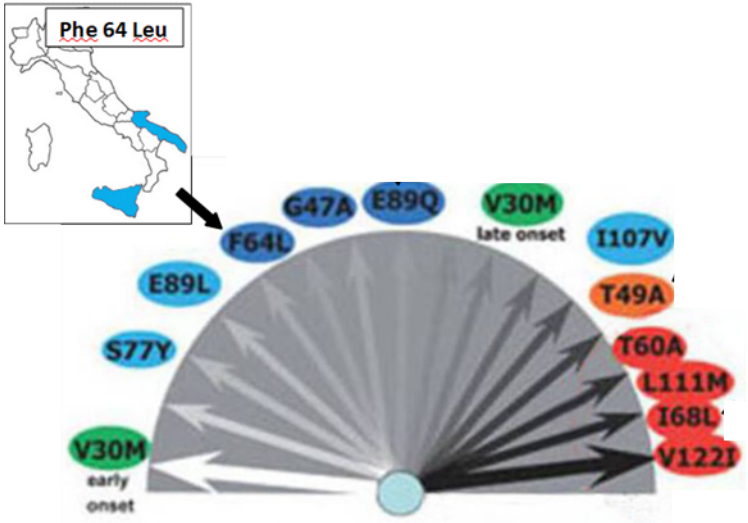
- Late onset
- Mainly characterized by a sensory polyneuropathy
- During its course heart and autonomic involvement



F64L in Italy

Firstly described in an American patient of Italian ancestry.

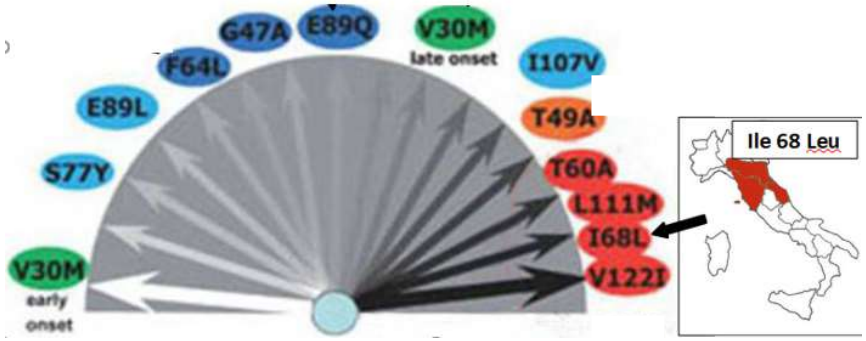
- Mainly neuropathic variant
- Patients usually have a late onset
- High number of sporadic patients and a long diagnostic delay (misdiagnosed with other peripheral neuropathies)



I68L in Italy

The percentage of patients carrying cardiological mutations is higher than that recorded in the past in Italy and in Western Europe countries.

- Cardiological phenotype
- Shortest disease duration
- Fast course and high mortality
  (41% at 3 yy and 63% at 5 yy)



Italy: the Italian Registry

Table 1. Clinical characteristics.

	Total	I68L	F64L	V30M	E89Q	V122I	Y78F	T49A
Number of symptomatic patients	260	47	58	60	33	13	13	10
%	100	18.1	22.3	23.1	12.7	5.0	5.0	3.5
Male/female ratio	2.3/1	2.6/1	3.8/1	3/1	1.3/1	3.3/1	12/1	0.8/1
Mean age (years)	67.1	72.4	70.2	66.2	58.5	73.7	72.6	49.4
Age range (yrs)	30–87	56–82	44–86	44–87	43–79	64–87	61–87	30–64
Mean age at the onset (years)	60.3	67.9	63.7	58.9	50.5	67.5	64.1	43.9
Age range at the onset (years)	29–82	47–79	42–80	31–81	37–70	56–82	55–81	30–55
Number of late onset (≥50 years)	216	45	56	48	18	13	13	2
%	83.1	95.7	96.6	80	54,5	100	100	20.0
Disease duration (mean ± SD; years)	6.8 ± 4.7	4.5 ± 2.4	6.5 ± 4.4	7.2 ± 5.2	8.0 ± 4.4	6.2 ± 4.2	8.5 ± 5.0	5.5 ± 3.4
Probands	163	31	42	42	11	12	10	0
Mean age at diagnosis in probands (years)	66.4	69.8	65.7	62.6	55.0	71.5	70.0	NA
Duration of symptoms at diagnosis in probands (years)	3.4	3.3	3.8	3.2	2.3	3	3.9	N.A.
Mean age at diagnosis in non-probands (years)	56.3	67.4	58.7	59.2	50.7	63	63.3	43.9
Duration of symptoms at diagnosis in non-probands (years)	1.2	0.6	1.3	1.4	1.3	0.5	6.0	0
Prevalent phenotype at onset	P	C	P	P	P	C	P	DYS
Most frequent onset symptom		Dyspnea	Paresthesia in LI	Paresthesia in LL	CTS	Dyspnea	Paresthesia in LL	Weightloss
Phenotype at prevalence day		P+	P+++	P+++	P++	P++	P+++	P++
		C+++	C+	C+	C++	C+++	C+	C++
		Dys +	Dys +	Dys +	Dys ++	Dys +	Dys +	Dys +++
Only heart involvement	35 (13.5%)							
FAP stage 1	137 (52.6%)							
FAP stage 2	53 (20.4%)							
FAP stage 3	35 (13.5%)							
Italian region of birth with highest prevalence	Sicily	Emilia Romagna	Apulia	Lazio	Sicily	Tuscany	Lombardy	Sicily
Number of asymptomatic carriers	187	53	33	30	19	21	3	3
%	100	28.3	17.6	16.0	10.1	11.2	1.6	1.6
Male/female ratio	0.7/1	1.1/1	0.7/1	0.7/1	0.7/1	0.4/1	0/1	0.5/1
Mean age (years)	52.3	54.8	56.8	48.3	46.2	55.7	53.3	40.0
Age range (years)	24–89	24–89	37–85	26–69	27–64	37–83	50–59	35–47

P: sensory-motor polyneuropathy; C: cardiomyopathy; DYS: dysautonomia; LL: lower limbs; +: mild (not clinically significant) ++: moderate (clinically relevant); +++: severe (clinically predominant); NA: not applicable.

What about Tuscany?

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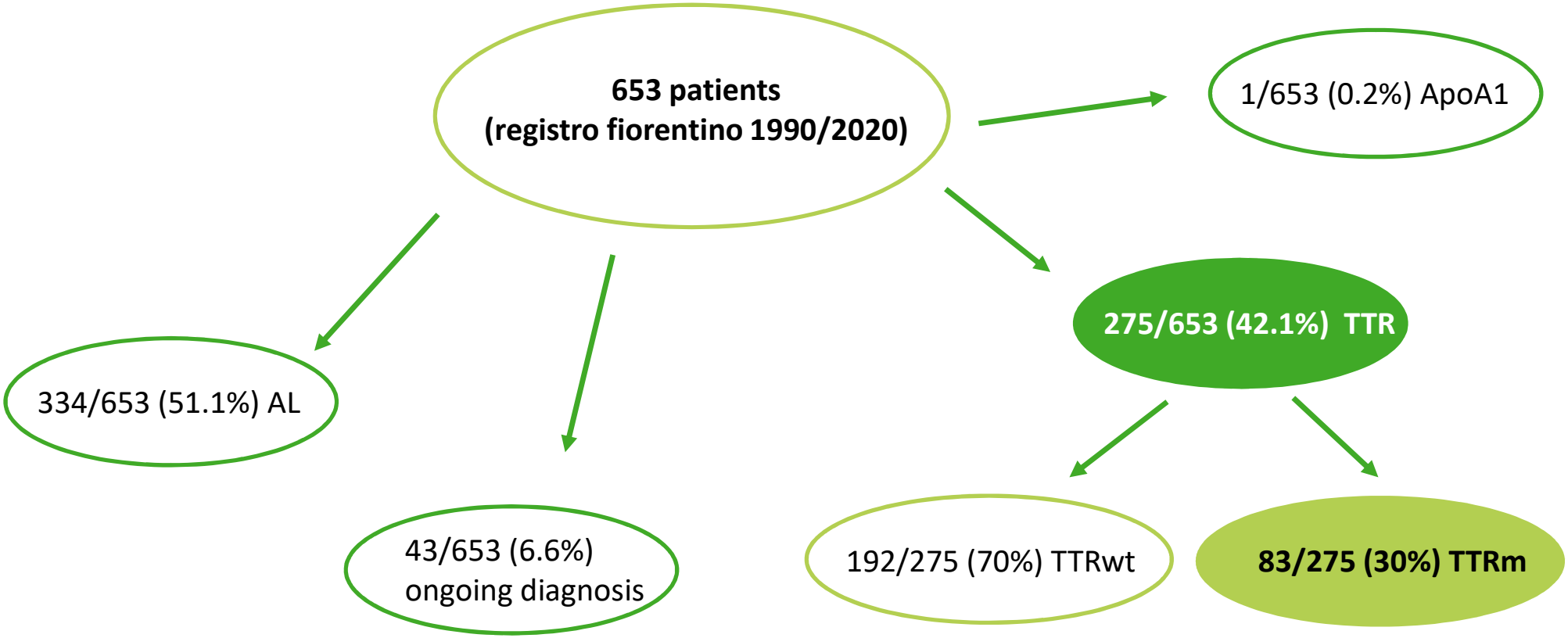

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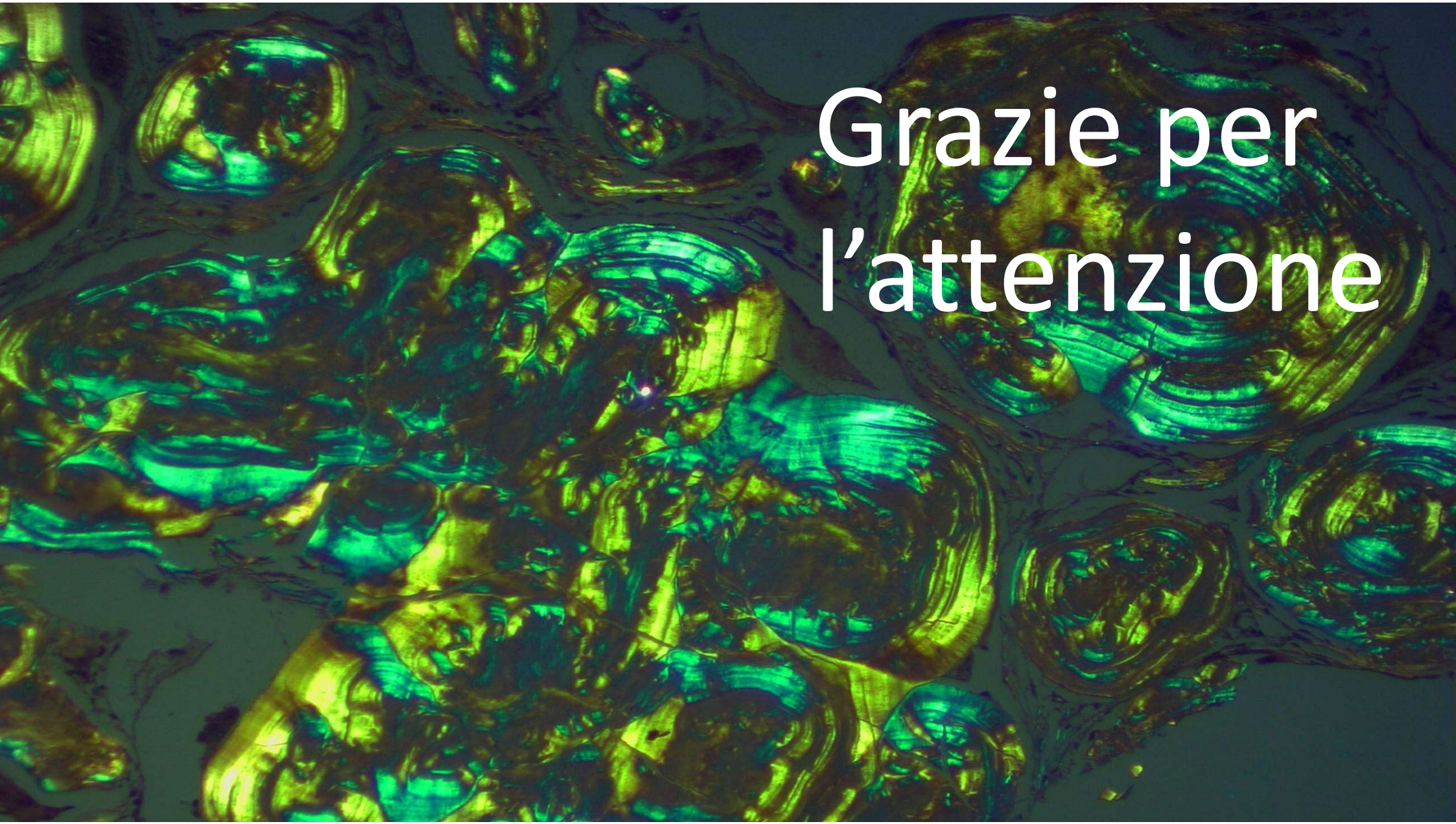
mutazione	N°pazienti	impegno	Provenienza
Ile68leu	**35**	**Cuore**	**Toscana**
Val122leu	**14**	**Cuore**	**Toscana**
Val30met	**2**	**Pnp/cuore**	**Toscana/Lazio**
Phe64leu	**3**	**Pnp/SNA/Cuore**	**Puglia/Calabria**
Gly57arg	2	**Cuore**/pnp lieve(subclinica)	Toscana
Gly47glu	3	**Cuore/pnp/Sna/gastro**	Toscana
Glu89lys	**1**	**Cuore**	**Toscana**
Glu54val	**1**	**Cuore**	**Toscana**
Phe64ile	**1**	**Cuore**	**Toscana**
Glu54lys	**4**	**Pnp/SNA/occhio/meningi?**	**Campania**
gly67ala	**1**	**Cuore**	**Romania**
Phe84Ile	**1**	**Cuore /PNP/SNA**	**Toscana**

Impegno neurologico in Toscana <5 % dei pazienti


Grazie per
l’attenzione