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ARiA VIII Symposium

Advances and Research in ATTR Amyloidosis

Genetic Testing: Value and modern approaches

> Dr. Paul A. van der Zwaag
Clinical Geneticist
Groningen Amyloidosis Center of Expertise
University Medical Center Groningen
The Netherlands

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GrACE
Groningen Amyloidosis Center of Expertise

Disclosures?

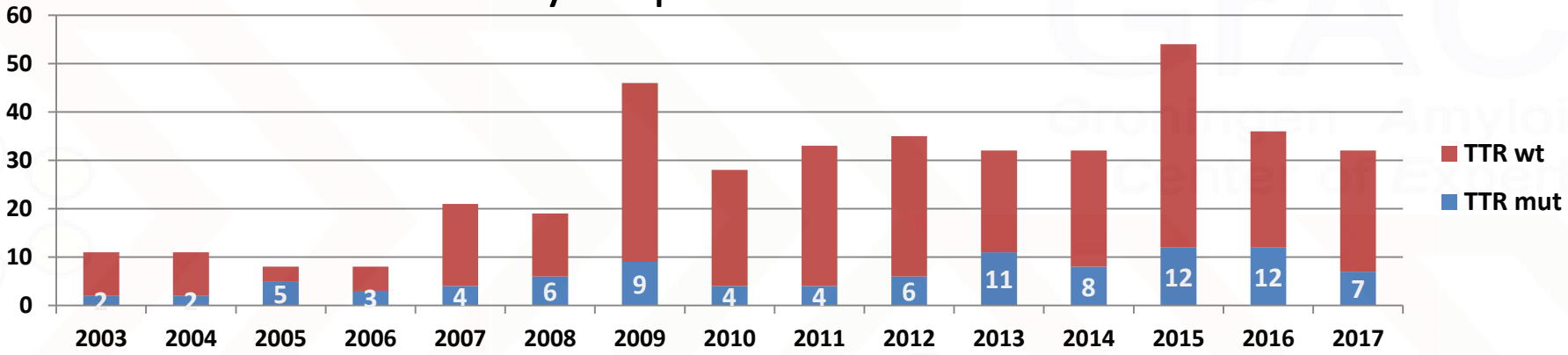
> To discuss with Pfizer/Synergy what's obligatory

> No additional disclosures

Genetic testing: background

> Sanger sequencing of *TTR* gene started in 1995 in UMCG
  - Genetic testing is covered by healthcare insurance in the Netherlands

> over 500 *TTR* analyses performed



Genetic testing: background

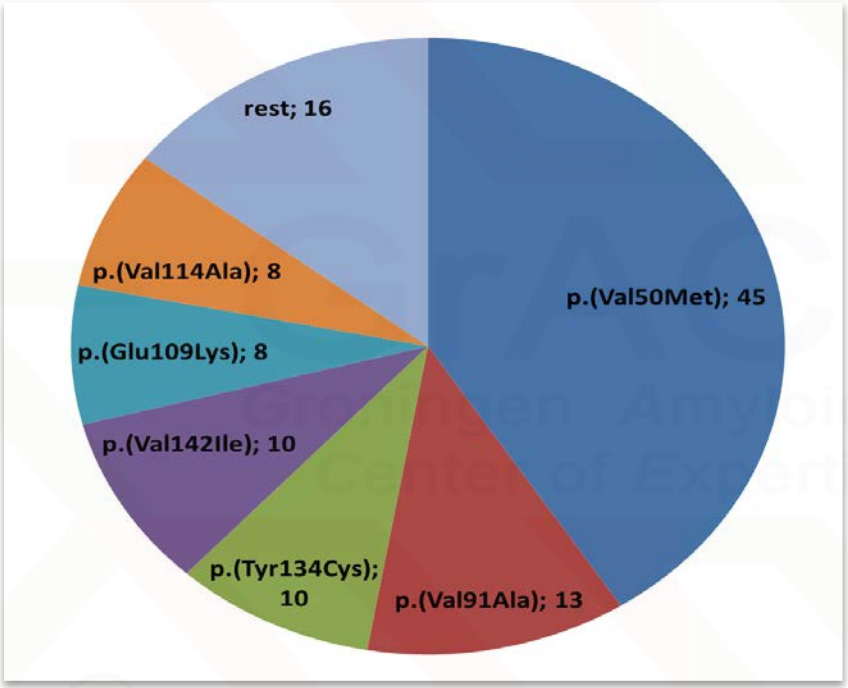
> 18 unique *TTR* variants identified in 110 patients

> 52 families:

- Largest family: 13 cases
- 35 single cases

> New nomenclature:

- **p.(Val50Met) = Val30Met**



Genetic testing: modern approach

> Amyloidosis gene panel introduced in 2017

- *APOA1, APOA2, APOC2, APOC3, B2M, CST3, FGA, GSN, IL31RA, LYZ, OSMR, TTR*

> 58 probands sequenced

- 3 pathogenic variants identified
  - > 2 in TTR [p.(Val50Met) and p.(Val142Ile)], 1 in APOA1
- 4 variants of unknown significance identified
  - > In APOC3, IL31RA and GSN (2x)
- Mean turn-around-time 31 days (range 15-45 days)

Genetic testing: modern approach

> *TTR* gene also present on cardiomyopathy panel

> 6 *TTR* variants identified in 2002 cardiomyopathy samples

- **c.148G>A p.(Val50Met) Pathogenic**
- **c.424G>A p.(Val142Ile) Pathogenic**
- c.127A>C p.(Ser43Arg) Likely pathogenic
- c.280G>C p.(Asp94His) [2x] Variant of unknown significance
- c.355G>A p.(Asp119Asn) Variant of unknown significance

Genetic testing: value

> Differentiate between ATTR and other amyloidosis subtypes

> Differentiate between wild-type and inherited ATTR amyloidosis

> Genotype-phenotype correlations

> Cascade family screening

Genetic testing: value

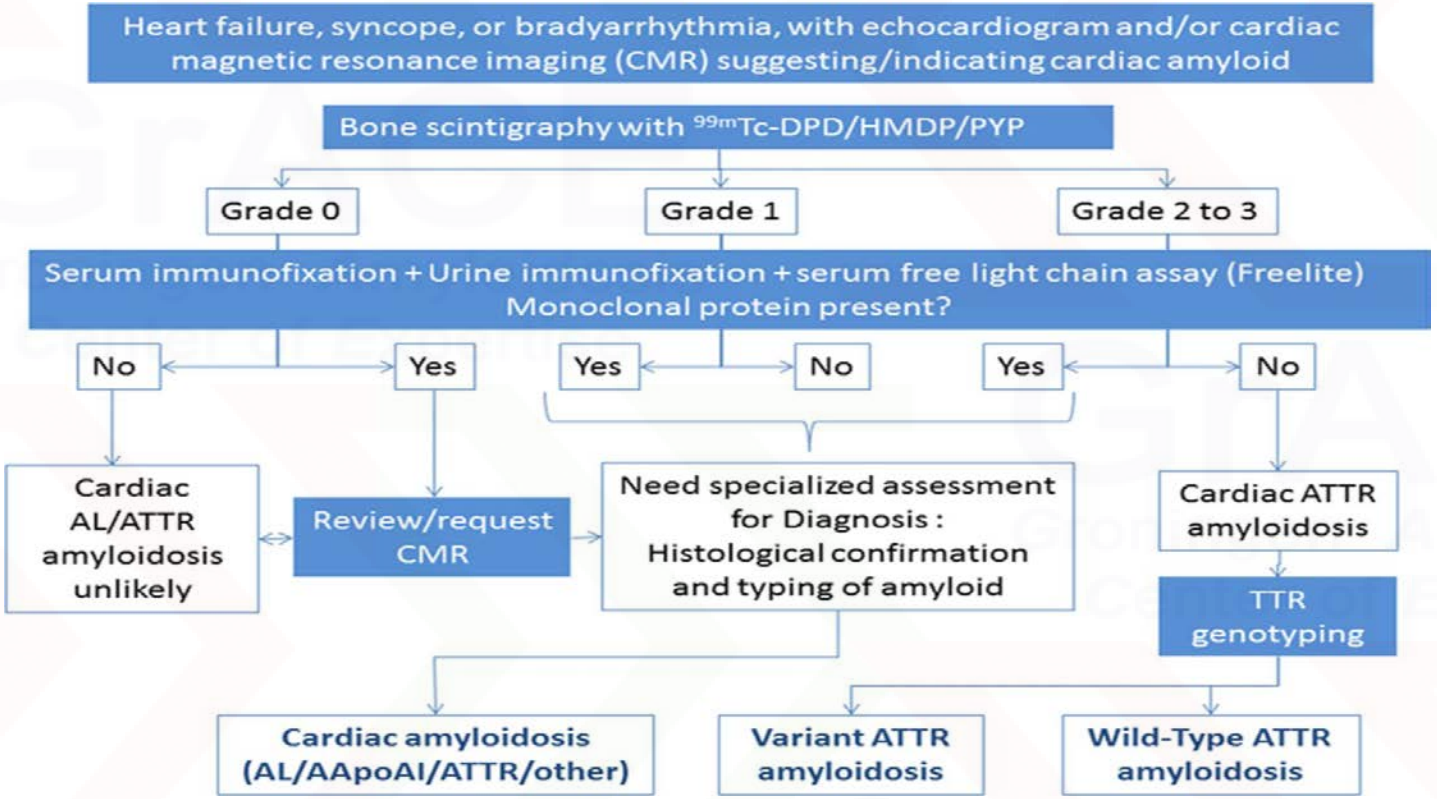
> Differentiate between ATTR and other amyloidosis subtypes

> Bone scintigraphy with

^{99m}Tc-DPD/HMDP/PYP grade 1-3

- Not ATTR specific:
- ApoAI p.Gln172Pro[1] (figure →)
- ApoAI p.Leu174Ser[2]
- ApoAII p.Arg78*[3]

1. Amyloid 2015;22: 252-3
2. Amyloid 2013;20:48-51
3. Kidney Intl 2003;64:11-6



Gillmore et al. Circulation 2016;133:2404-12

Genetic testing: value

> Differentiate between ATTR and other amyloidosis subtypes

> Differentiate between wild-type and inherited ATTR amyloidosis

Wild-type ATTR amyloidosis	Hereditary ATTR amyloidosis
Hypertrophic cardiomyopathy, carpal tunnel syndrome, spinal stenosis	Polyneuropathy and/or cardiomyopathy
Tendon ruptures	Autonomic neuropathy, eye/brain involvement
Sporadic, males > females, onset often >60yr	Autosomal dominant, onset and prognosis highly variable and mutation dependant

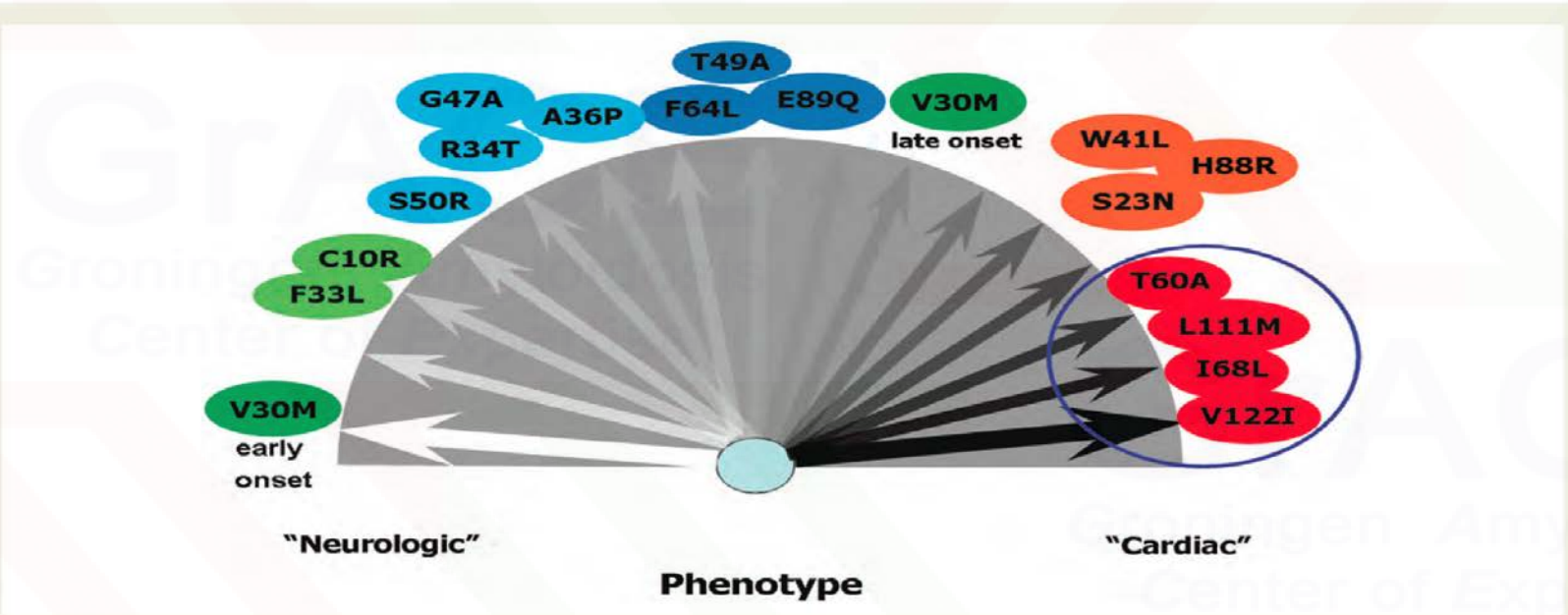


Figure 2 Possible spectrum of genotype–phenotype correlations in transthyretin-related amyloidosis. Phenotypic expression of transthyretin-related amyloidosis varies widely from an almost exclusively neurological involvement (Val30Met mutation with early-onset disease) to a predominant or exclusively cardiac involvement (Thr60Ala, Leu111Met, Ile68Leu, and Val122Ile mutations). In between, several transthyretin-related amyloidosis mutations are associated with variable degrees of neurological and cardiological involvement, including Val30Met with late-onset disease.

Rapezzi et al. Eur Heart J 2013;34:520-8

Genetic testing: value

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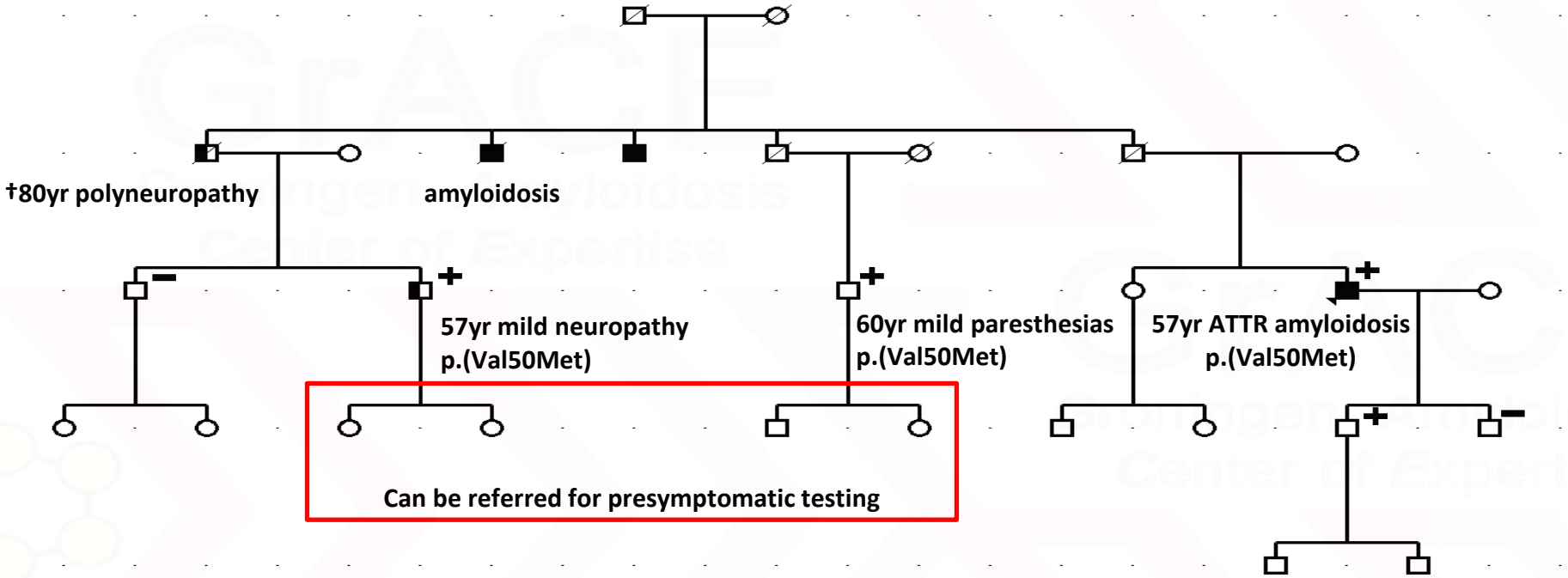
> Genotype-phenotype correlations

> Cascade family screening


†80yr polyneuropathy
amyloidosis
57yr mild neuropathy
p.(Val50Met)
60yr mild paresthesias
p.(Val50Met)
57yr ATTR amyloidosis
p.(Val50Met)
Can be referred for presymptomatic testing

Genetic testing: value

> Differentiate between ATTR and other amyloidosis subtypes

> Differentiate between wild-type and inherited ATTR amyloidosis

> Genotype-phenotype correlations

> Cascade family screening

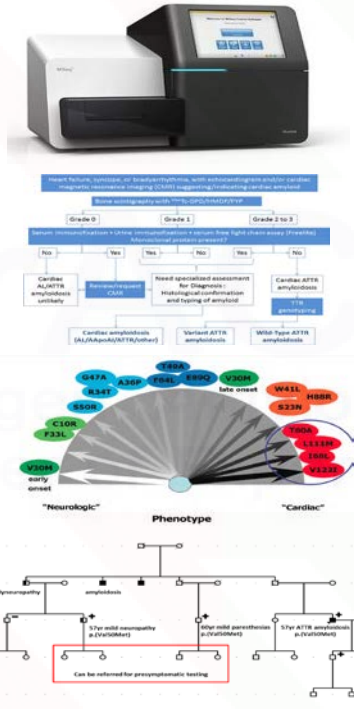
- Presymptomatic testing after genetic counselling
- Prevents diagnostic delay and enables early start of treatment
- Non-carriers can be reassured
- Screening of potential related liver donors

Genetic testing: value & modern approaches

> Differentiate between ATTR and other amyloidosis subtypes

> Differentiate between wild-type and inherited ATTR amyloidosis

> Genotype-phenotype correlations



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Questions?