

# The Diflunisal Trial

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# **Familial Amyloid Polyneuropathy**

- Basis:** Misfolding of variant transthyretin (TTR)
- Factory:** Liver, eye, brain
- Genetics:** Autosomal dominant inheritance
- Features:** Sensory and motor peripheral neuropathy  
Autonomic neuropathy  
    orthostasis  
    GI dysmotility  
Infiltrative cardiomyopathy  
Renal disease
- Outcome:** Death 7-15 years after presentation

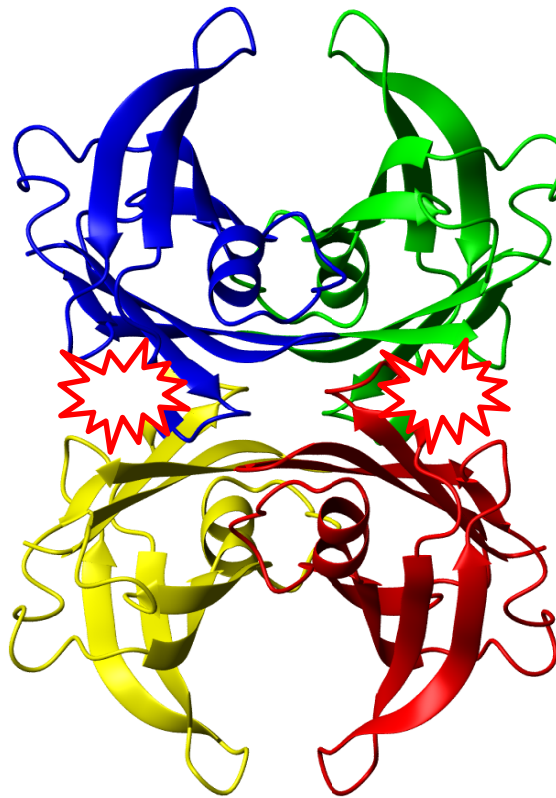
# Transthyretin (TTR)



Trans =

thy =

retin =



transport

thyroid hormone

retinoic acid

# Gene therapy: Liver Transplantation

- 1990 Karolinska Institute, Sweden
- 1991 Deaconess Hospital, Boston MA
- FAP World Transplant Registry: 20-year experience
  - 1789 OLT (FAPWTR : 31 December 2009)
  - 92.3% 5-year survival (Am J Transplant 2007)
  - 46 variant TTR genotypes
  - 19 OLT + OHT

# Post Liver Transplant Problems

## Progressive heart thickening

1997 Dubrey et al (Transplantation 64:74-80)

- 45% increasing LVH – non-V30M

2002 Olofsson et al (Transplantation)

- V30M ATTR patients

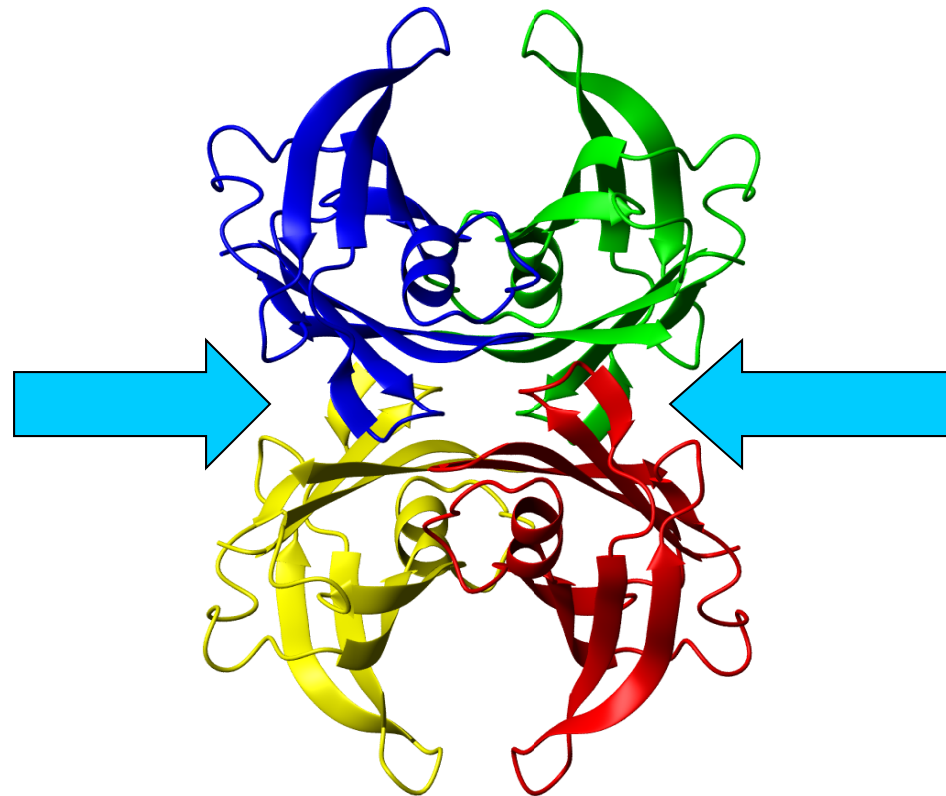
## Ocular disease

## Arrhythmias

## Peripheral neuropathy



# Transthyretin (TTR)





# Diflunisal (Dolobid) IND 68092



- modified aspirin-like chemical
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High blood concentrations and minimal side effects





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- Genetics:** Autosomal dominant inheritance  
> 100 variant TTR genes – destabilize tetramer
- Features:** **Sensory and motor peripheral neuropathy**  
**Autonomic neuropathy**  
orthostasis  
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# Peripheral Neuropathy in FAP

Disease model: **Peripheral neuropathy in diabetes mellitus**

Microscopic tissue changes

Peripheral & autonomic neuropathies

Neurologic Impairment Score + 7 (NIS+7) : Peter Dyck, Mayo Clinic

Nerve Conduction Velocities

Computer driven Sensory Testing

Muscle strength & Reflex Assessment

Heart rate variation with deep breathing

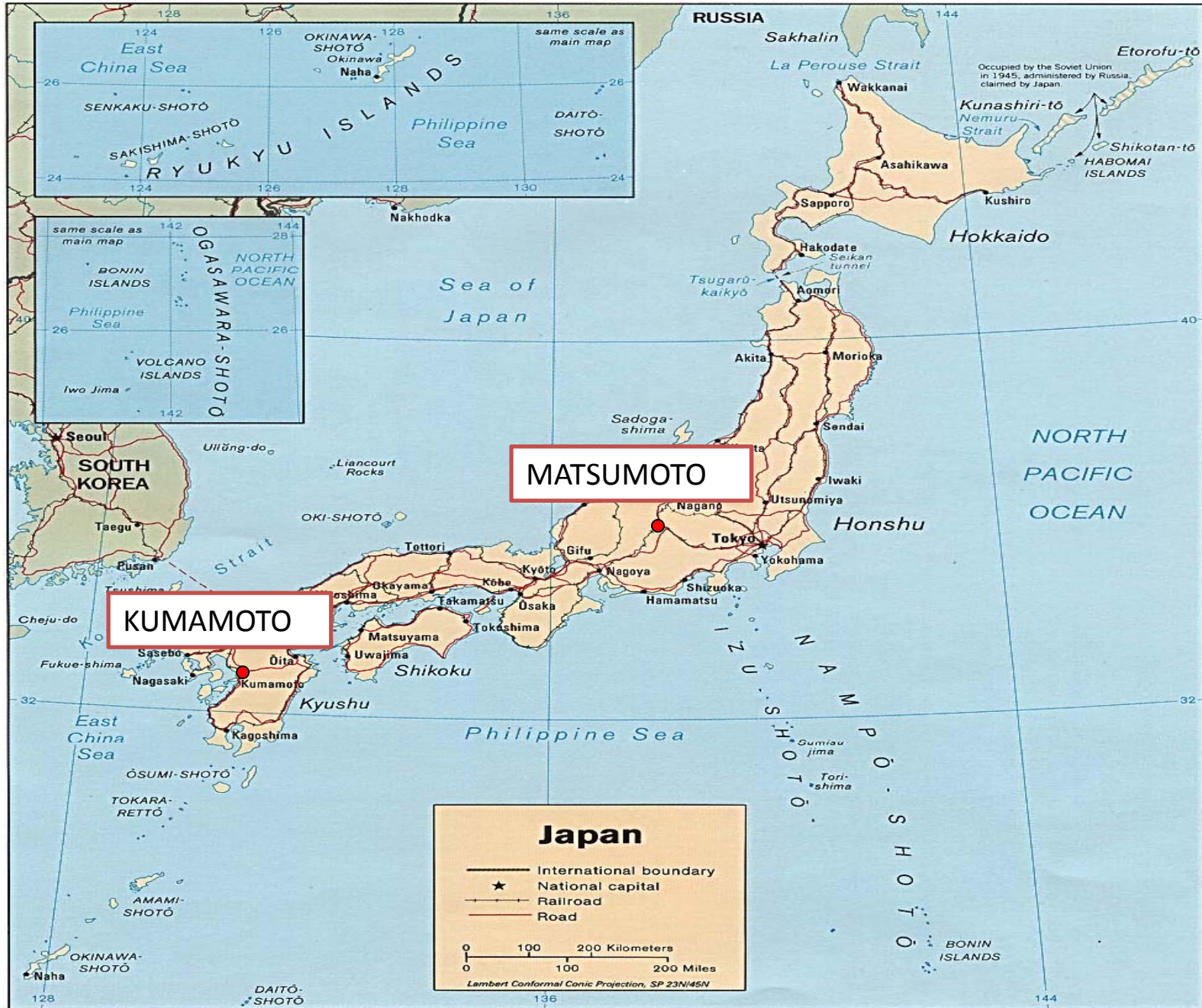
# EUROPE



Scale 1: 19,500,000  
Lambert Conformal Conic Projection,  
standard parallels 40°N and 56°N

Boundary representation is not necessarily authoritative.







**ROCHESTER**

**BOSTON**

**NEW YORK**



# Clinical Trials



- Autosomal dominant genetics = family disease
- Participating in a clinical trial
  - Close follow up by disease experts
  - Careful monitoring of drug effects & side-effects
  - Collection and analysis of data → approved new Rx



# CONCLUSIONS



- Get tested -- know your genetics
- Be part of the solution → participate in trials
- Encourage your physicians to contact FAP experts and refer to amyloid programs