

PROPOSITIONS

Genetics of Pompe Disease

The secrets within the coding region of the *GAA* gene and beyond

1. "Extended analyses are essential to detect new disease-associated *GAA* variants and non-Mendelian genotypes when conventional procedures fail to confirm Pompe disease." (This thesis)
2. "The use of Next Generation Sequencing (NGS) as a routine procedure combined with Newborn screening (NBS) has the potential to detect patients at high risk and ensure adequate genetic counselling of parents and timely start of treatment." (This thesis)
3. "Curated disease-specific databases such as the Pompe disease *GAA* variant database (www.pompevariantdatabase.nl) provides guidance to clinicians and clinical geneticists in establishing an accurate molecular diagnosis and counselling of patients and their families." (This thesis)
4. "The effect of disease-associated variants in the *GAA* gene depends on their haplotype context." (This thesis)
5. "The identification of factors that modify the clinical course of Pompe disease will substantially contribute to the understanding of clinical diversity, may lead to the discovery of disease-specific biomarkers, and the discovery of therapeutic targets." (This thesis)
6. "Purifying selection acts more strongly against haplotype configurations that decrease functional gene dosage while acting more weakly on those that increase functional gene dosage." (Adapted from Castel, S.E. *et al.*, Nat Genet, 2018)
7. "Medical genetics must be a compulsory discipline in all medical courses, aiming to provide physicians with basic training in genetics to prevent late diagnosis of inherited diseases and provide a follow up in primary care." (Adapted from Iriart, J.A.B. *et al.* Cien Saude Colet, 2019)
8. "In 2030, generating and analysing a complete human genome sequence will be routine for medical diagnostics, becoming as straightforward as carrying out a DNA purification." (Adapted from Green, E.D. *et al.*, Nature, 2020)
9. "Your genetics is not your destiny." (George McDonald Church)
10. "Doe het voor de patiënten, want daar gaat het om!" "Do it for the patients because that's what it's all about!" (Robert Hofstra)
11. "A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty." (Winston Churchill)

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