Expanding the mutation spectrum in FSHD and ICF syndrome

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Stellingen behorende bij het proefschrift

EXPANDING THE MUTATION SPECTRUM IN FSHD AND ICF SYNDROME

1. Recessive mutations in *DNMT3B* cause ICF1 syndrome, dominant mutations in *DNMT3B* combined with medium-short permissive D4Z4 repeat arrays can cause FSHD2 (this thesis)

2. FSHD1 and FSHD2 represent opposite extremes of a disease continuum (this thesis)

3. D4Z4 methylation has predictive value for determining the functional consequences of *SMCHD1* variants of unknown significance (this thesis)

4. In the absence of exonic *SMCHD1* variants in FSHD2 patients, it is important to screen for *SMCHD1* hemizygosity or intronic *SMCHD1* variants (this thesis).

5. The gender bias in ICF2 patients suggests that pathogenic ZBTB24 variants are more deleterious for females. (this thesis)

6. Concerning D4Z4 and DUX4: More is less (Adapted from P.E. Thijssen, Thesis, Leiden University, 2016)

7. To find novel deep intronic mutations and determine their pathogenicity it is crucial to combine sequencing of intronic regions with studies addressing the mRNA molecules produced in affected tissue from patients. (Drago et al. Hum Genet 2017)

8. Mutations in *SMCHD1* thus contribute to distinct phenotypic spectra, from craniofacial malformation and reproductive disorders to muscular dystrophy, which we speculate to be consistent with oligogenic mechanisms resulting in pleiotropic outcomes. (Shaw et al. Nat Genet 2017)

9. The complex, but highly overlapping, pathophysiology suggests that all ICF genes act in common or converging pathways involved in immunity, chromatin regulation and development. (Thijssen et al. Nat Com 2015)

10. Determining the epigenetic signatures that are predictive of disease severity and identifying the spectrum of disease modifiers in FSHD are vital to the development of effective therapies. (Himeda et al. Antioxid. Redox Signal. 2015)