

Natural history in LGMD- uncharted waters?



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Pitfalls in defining the natural history of LGMD

- LGMD is not a single disorder (1A-F, 2A-J)
- Early reports on LGMD included a variety of diseases
 - Anything predating full molecular analysis of patient cohorts is of dubious value
 - Molecular analysis is so newly available that longitudinal studies have not been possible
- Full molecular diagnosis of LGMD is still not widely available
- All types of LGMD are individually rare

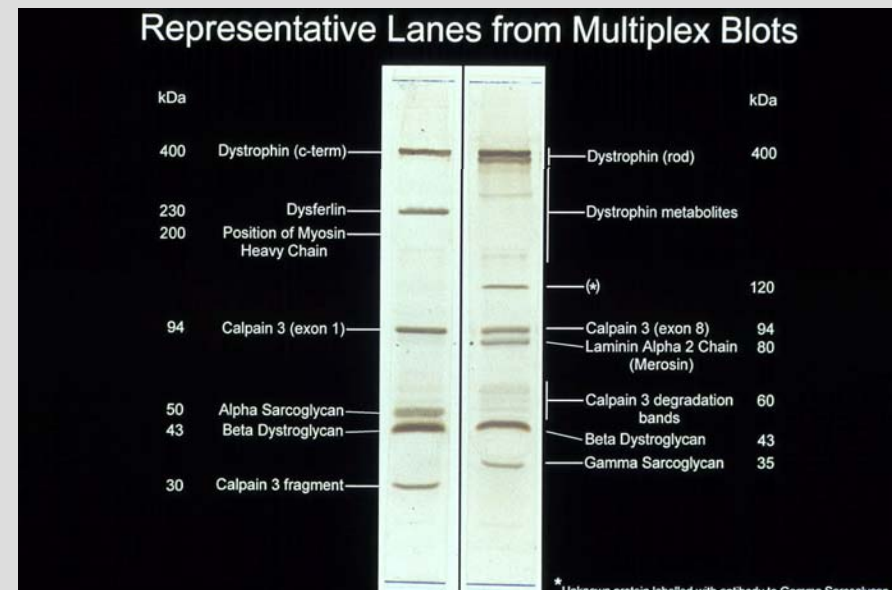
Our clinic population (1000 patients)

- 33% myotonic dystrophy
- 25% DMD/BMD
- 10% FSHD
- 7.5% SMA
- **5% LGMD**
- 3% each Bethlem, congenital muscular dystrophy, congenital myopathies



LGMD subtypes in the North of England

- LGMD2I 27%
- LGMD2A 14%
- Sarcoglycanopathy 11%
- Lamin A/C 11%
- LGMD2B 2%
- All above excluded 34%



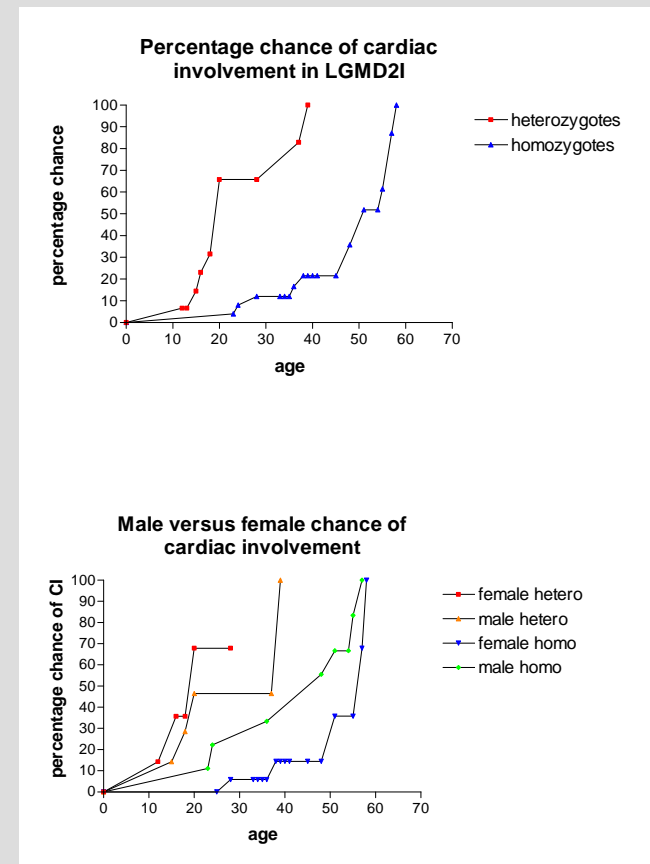
Keeping the LGMD subtypes distinct does matter

- Eg 1: Pattern of muscle involvement
- Which muscles chosen for composite scores will make a difference
- Little formal comparative data exist



Keeping the LGMD subtypes distinct does matter

- Eg 2: incidence of complications
- Cardiac and respiratory complications in LGMD2I, SCG
- Cardiac complications in LGMD1B
- Little formal comparative data exist



Even within the subtypes there is variability.....

- Especially in rate of progression
- Can some improve for a while (eg Cav3?)
- Genotype phenotype correlations appear to add little to understanding of variable severity

To facilitate trials

- Need for standards of diagnosis and funded international referral centres?
 - In the meantime a registry of where such diagnostic tests are available
- Standardised data collection on well characterised patient cohorts?
 - But would take years for longitudinal data to emerge

In the meantime.....

- Do we know today enough to embark on LGMD trials?
- Single issue trials in single diseases- yes
- Large scale trials encompassing many diseases- ?
 - Pragmatically many extrapolations can be made from other better characterised conditions
 - Can weakness, functional impairment and QOL issues be assessed regardless of underlying diagnosis?
 - Do we know enough about genotype-phenotype correlations to ensure that we can adequately match controls?