COMMON INHERITED METABOLIC CONDITIONS IN SOUTH AFRICA

DIAGNOSING “RARE” DISEASE IN GENETICALLY UNIQUE AND UNDERSTUDIED POPULATION GROUPS

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INHERITED METABOLIC DISEASES GROUP
UCT / NHLS
Clinical diagnosis
Clinicians

Biochemistry -
  amino acids, organic acids,
carnitines, VLCFAs etc
Red Cross Hospital - Chemistry

Tissue Culture +
specific enzyme assay
Metabolic lab – UCT

Genetic analysis
IMD molecular lab - GSH
OBJECTIVES

TO PRESENT COMBINED RARE DISEASE DATA FROM THE NATIONAL HEALTH LABORATORY SERVICES (NHLS) INHERITED METABOLIC DISEASE (IMD) LABORATORIES AT RXH AND GSH OVER THE PAST 10 YEARS

METHODS

DATA FROM IMD CASES WITH CONFIRMED DIAGNOSES WERE RETRIEVED FROM EXISTING DATABASES AT THE TWO REFERRAL CENTRES. ALL IDENTIFIABLE PATIENT INFO HAVE BEEN REMOVED.
GALACTOSAEMIA (N=45)

- p.S135L/p.S135L: 38 cases
- p.Q188R/p.S135L: 5 cases
- p.S135L/?: 2 cases
GLUTARIC ACIDURIA TYPE 1 (N=38)

- GCDH: p.A293T/p.A293T (4 cases)
- GCDH: p.A293T/? (2 cases)
- GCDH: p.A293T/p.His196Pro(VUS) (1 case)
CYSTINOSIS (N=~23)

- CTNS:c.971-12G>A/c.971-12G>A: 1
- CTNS:c.971-12G>A/c.18_21delGACT: 2
- CTNS:c.971-12G>A/c.809C>T: 19
- CTNS:c.971-12G>A/c.422C>T: 1

Legend:
- Square: CTNS:c.971-12G>A/c.971-12G>A
- Circle: CTNS:c.971-12G>A/c.18_21delGACT
- Diamond: CTNS:c.971-12G>A/c.809C>T
- Triangle: CTNS:c.971-12G>A/c.422C>T
MPV17 NEUROHEPATOPATHY
(See Poster #P13)

- MPV17:p.Q36X/p.Q36X
PRIMARY HYPEROXALURIA (N=10)

- AGXT p.A112D/p.A112D
- AGXT p.A112D/p.S158L
- AGXT c.445delG/c.445delG
- AGXT c.445delG/p.A112D
MTDNA CYTOPATHIES (N=46)
(See Poster #P14)

mtDNA mutations

- LHON
- MILS
- MELAS: m.3243A>G
- MERRF: m.8344
- NARP/Leigh: m.8993T>C/G
- Multiple deletions
- Large mtDNA deletions

LHON mutations
- m.11778G>A
- m.14484T>C
- m.3460G>A
- m.3635G>A

MILS mutations
- m.14459A>G
- m.13094T>C

Multiple deletions

11
15
12
3
1
3
10
2
OTC (N=12)

- OTC: Ex1del
- OTC: p.Pro347Leu
- OTC: p.Leu95Ser
- OTC: p.Asp196Thr
- OTC: p.Pro225Leu/
- OTC: del ex5-10
- OTC: p.Arg141Gly
- OTC: p.c.867+1G>T
X-LINKED ADRENOLEUKODYSTROPHY (N=10)

- ABCD1: p.R518Q
- ABCD1: p.R518QW
- ABCD1: p.R660P
- ABCD1: p.G512S
- ABCD1: p.S108L
- ABCD1: p.P543L
- ABCD1: p.Y174C
21-OH DEFICIENCY CAH (N=11)

- CYP21A2: 5` convers (incl ex 1)/compl gene del
- CYP21A2: 5` convers (incl ex 1)?Homozyg
- CYP21A2: p.Arg357Trp/conv ex 4-10
- CYP21A2: c.290-13C>G/CYP21A2*20K
- CYP21A2: p.Gln318X/Exon 6 cluster
- CYP21A2: p.R479L/?
CONCLUSIONS

Most commonly diagnosed IMDs (excl. CHT and CF):

- GA1
- Cystinosis
- Galactosaemia
- MPV17
- PH1
- MtDNA cytopathies:
  - MELAS
  - LHON
- Urea cycle defects (mainly OTC)
- Propionic Acidaemia
- CAH
- XALD
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Significantly amenable to treatment if diagnosed early
CONCLUSIONS

Most commonly diagnosed IMDs (excl. CHT and CF):

- **GA1** p.A293T 1:36 ; 1/5 184 newborns
- **Cystinosis** c.971-12G>A 1:50 ; 1/10 000 newborns
- **Galactosaemia** p.S135L 1:60 ; 1/14 400 newborns
- **MPV17** p.Q36X 1:68 ; 1/18 496 newborns
- **PH1** p.A112D ??

Significantly amenable to treatment if diagnosed early

- MtDNA cytopathies:
  - MELAS
  - LHON
- Urea cycle defects (mainly OTC)
- Propionic Acidaemia
- CAH
- XALD

- Genetics – With exception of mtDNA, X-linked disorders (OTC and XALD) and CAH, all have underlying mutations that are unique to South African populations

TAKE HOME MESSAGE

We should be careful in SA of using IMD incidence data from other countries or anecdotal evidence to direct how we employ limited resources in the field of rare diseases.

These data increasingly support our opinion that founder mutations and not consanguinity are responsible for the large proportion of recessive IMDs that we diagnose.