

COMMON INHERITED METABOLIC CONDITIONS IN SOUTH AFRICA

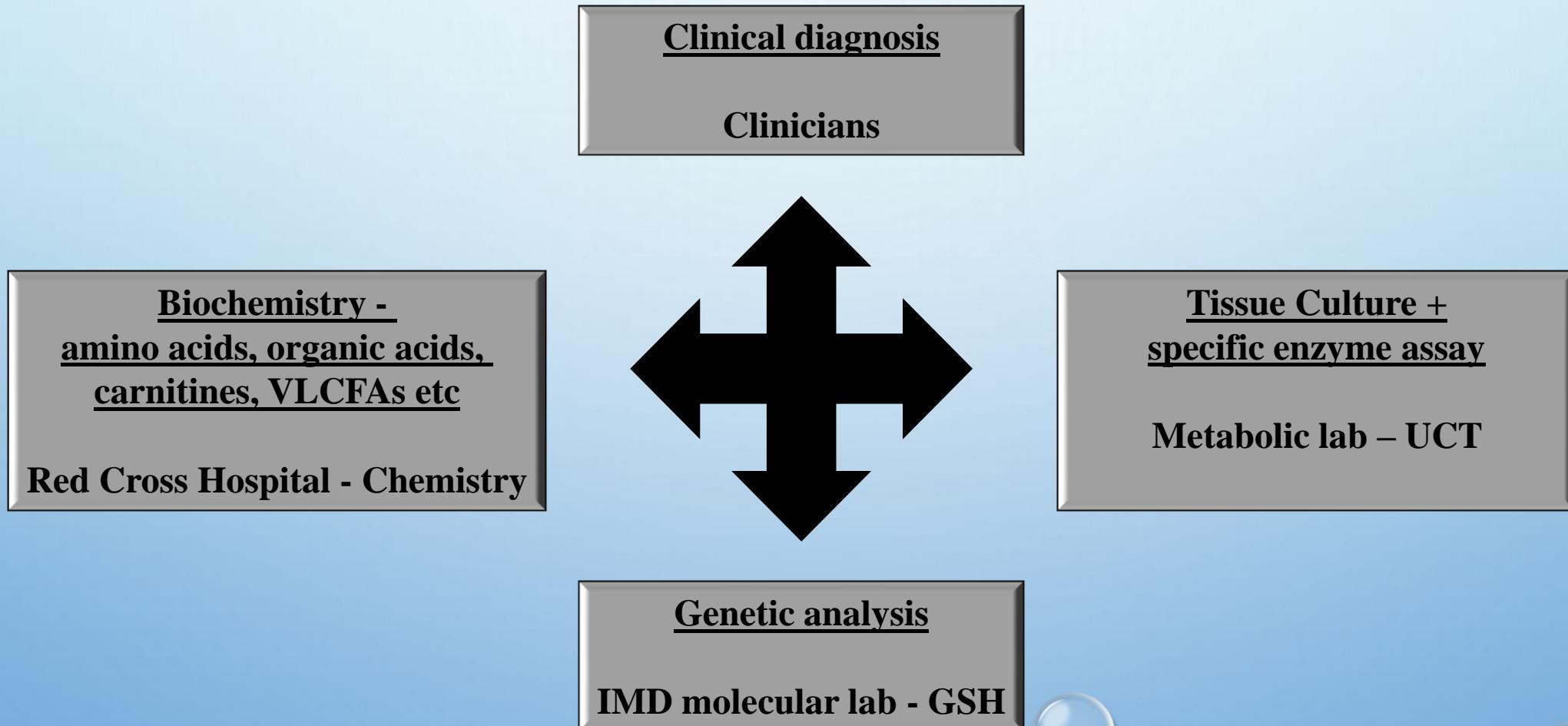
DIAGNOSING “RARE” DISEASE IN GENETICALLY UNIQUE AND UNDERSTUDIED POPULATION GROUPS



S MELDAU, G VAN DER WATT
INHERITED METABOLIC DISEASES GROUP
UCT / NHLS



NHLS/UCT INHERITED METABOLIC DISEASES GROUP

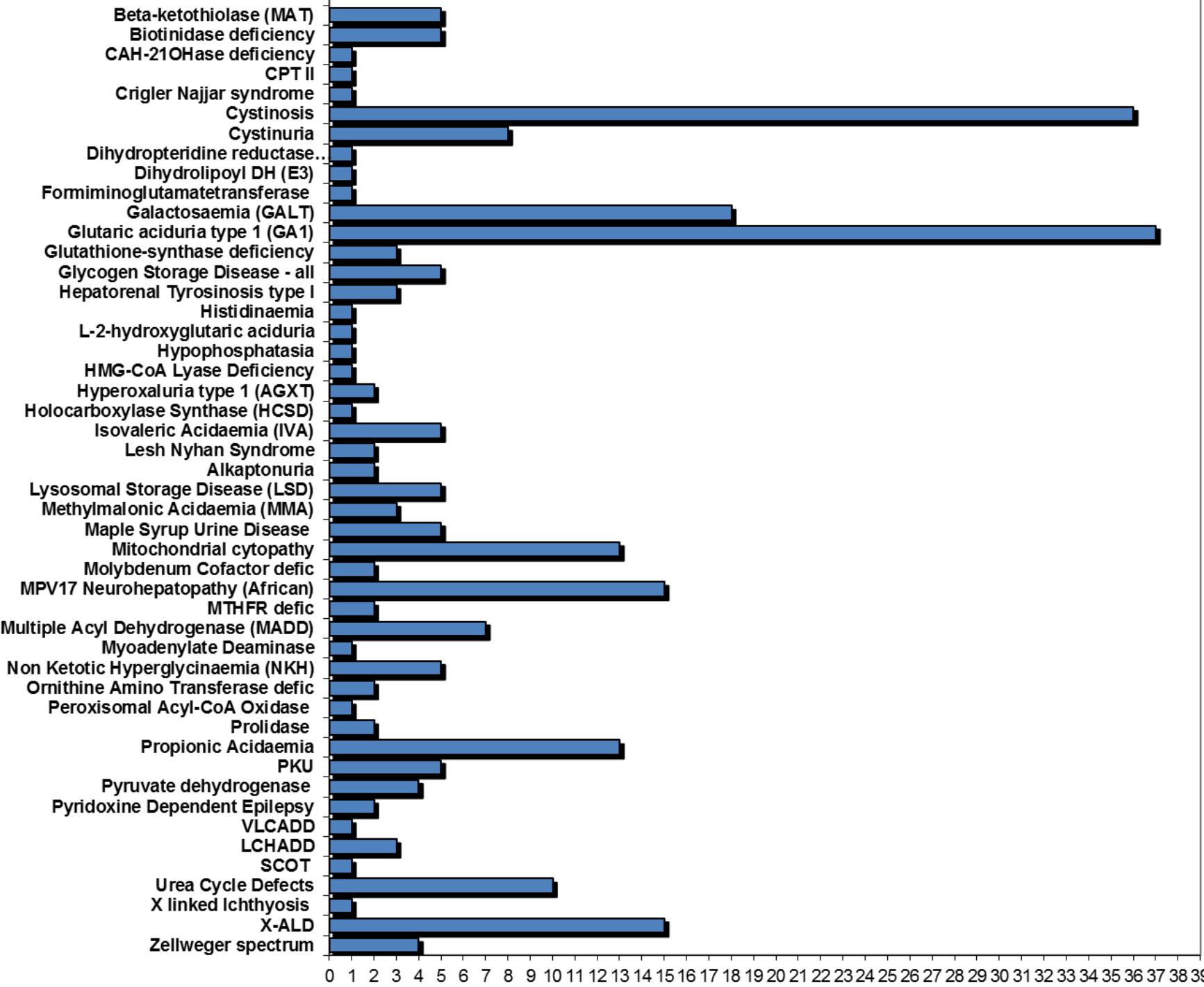


OBJECTIVES

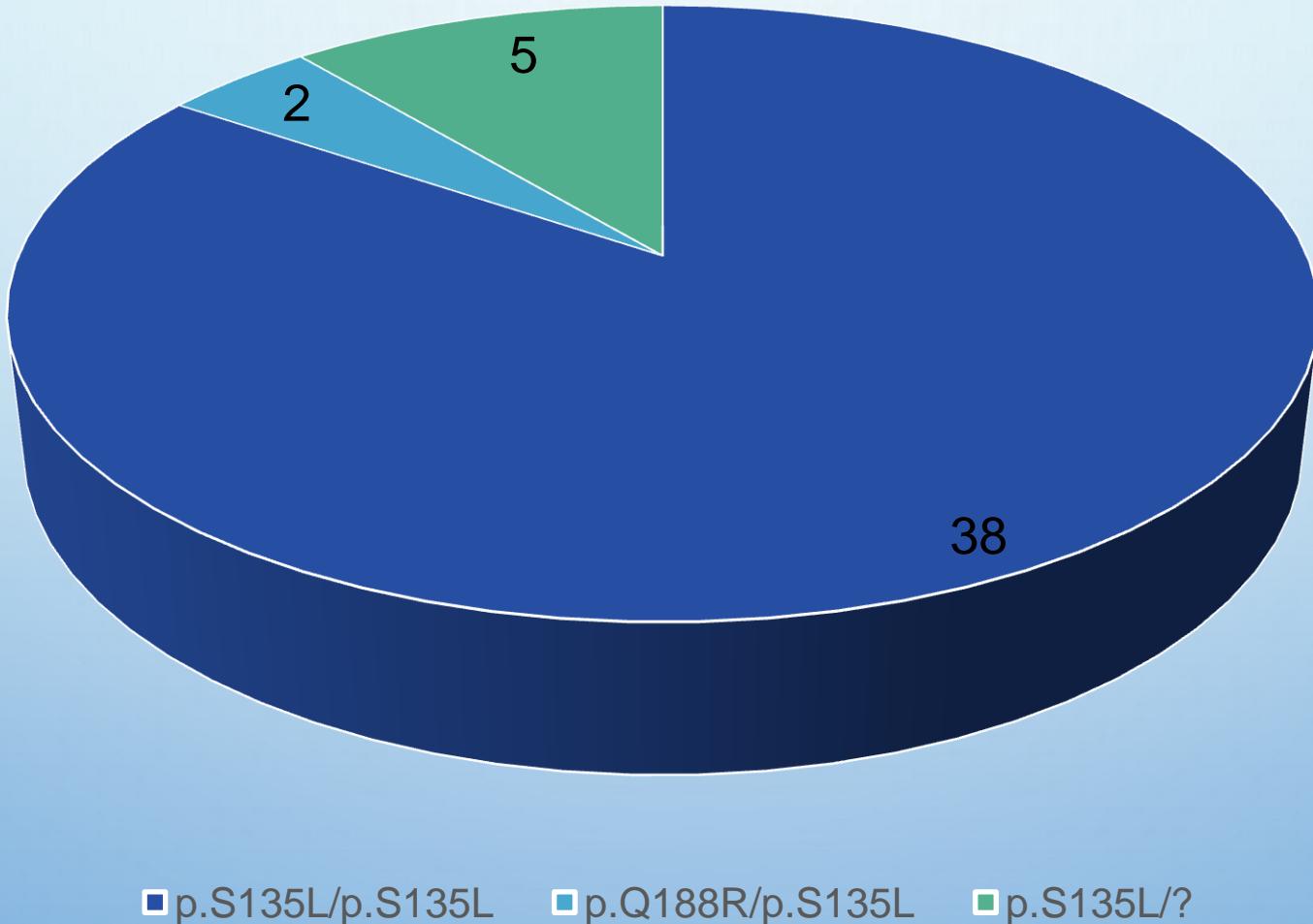
TO PRESENT COMBINED RARE DISEASE DATA FROM THE NATIONAL HEALTH LABORATORY SERVICES (N HLS) INHERITED METABOLIC DISEASE (IMD) LABORATORIES AT RXH AND GSH OVER THE PAST 10 YEARS

METHODS

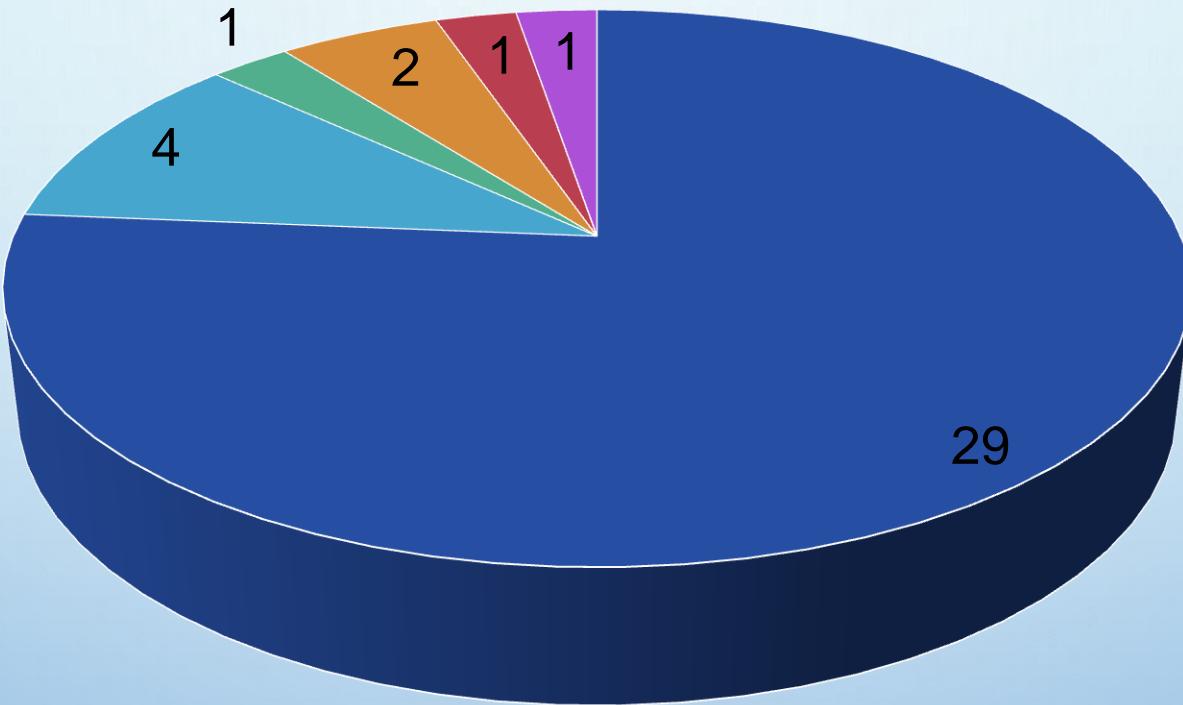
DATA FROM IMD CASES WITH CONFIRMED DIAGNOSES WERE RETRIEVED FROM EXISTING DATABASES AT THE TWO REFERRAL CENTRES. ALL IDENTIFIABLE PATIENT INFO HAVE BEEN REMOVED.



GALACTOSAEMIA (N=45)



GLUTARIC ACIDURIA TYPE 1 (N=38)



■ GCDH: p.A293T/p.A293T

■ GCDH: p.A293T/p.His196Pro(VUS)

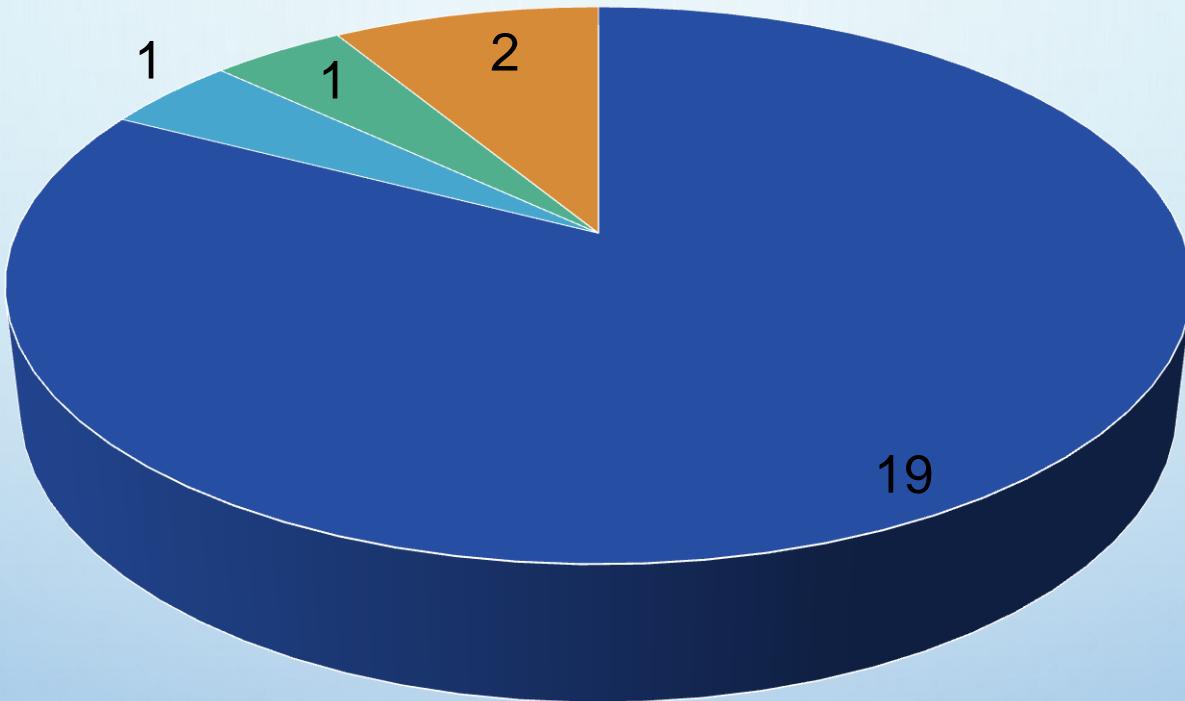
■ GCDH: p.Glu59Pro/p.Glu59Pro

■ GCDH: p.A293T/?

■ GCDH: p.A293T/p.R402W

■ GCDH: p.R355C/p.R383C

CYSTINOSIS (N=~23)



■ CTNS:c.971-12G>A/c.971-12G>A

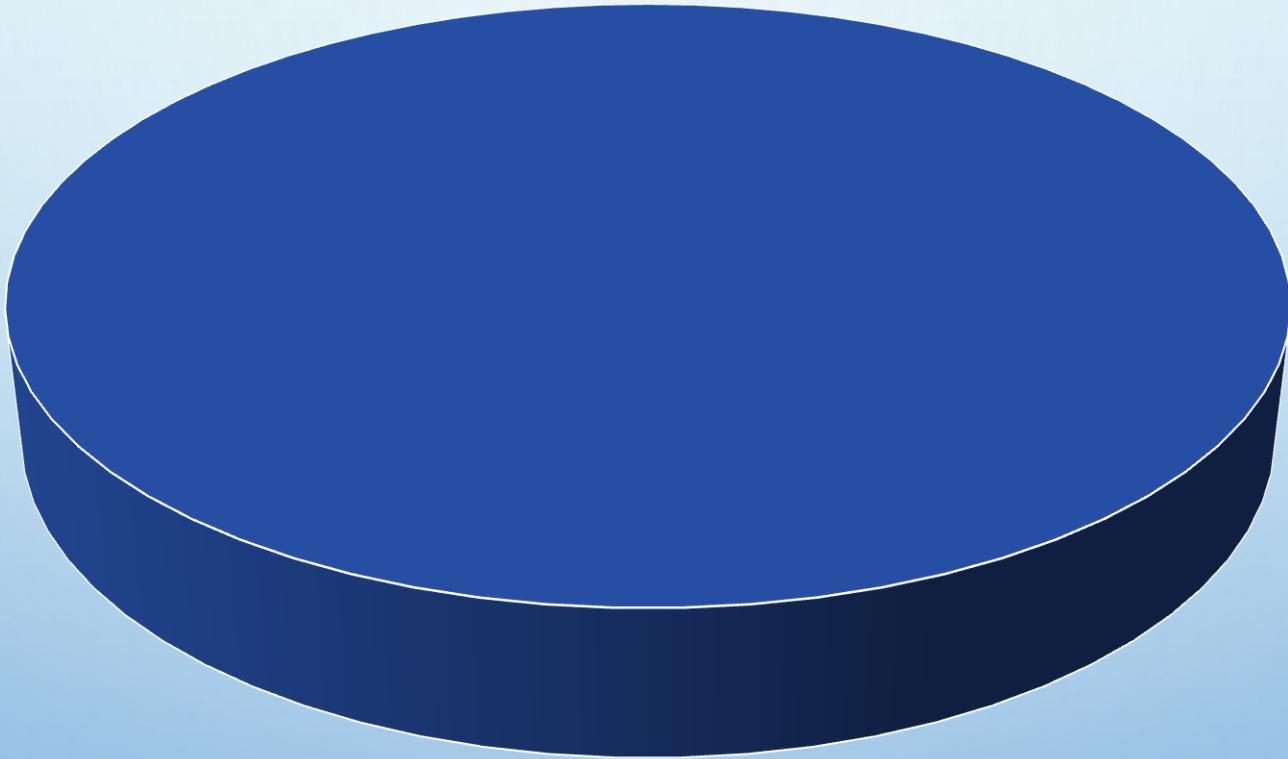
■ CTNS:c.971-12G>A/c.809C>T

■ CTNS:c.971-12G>A/c.18_21delGACT

■ CTNS:c.971-12G>A/c.422C>T

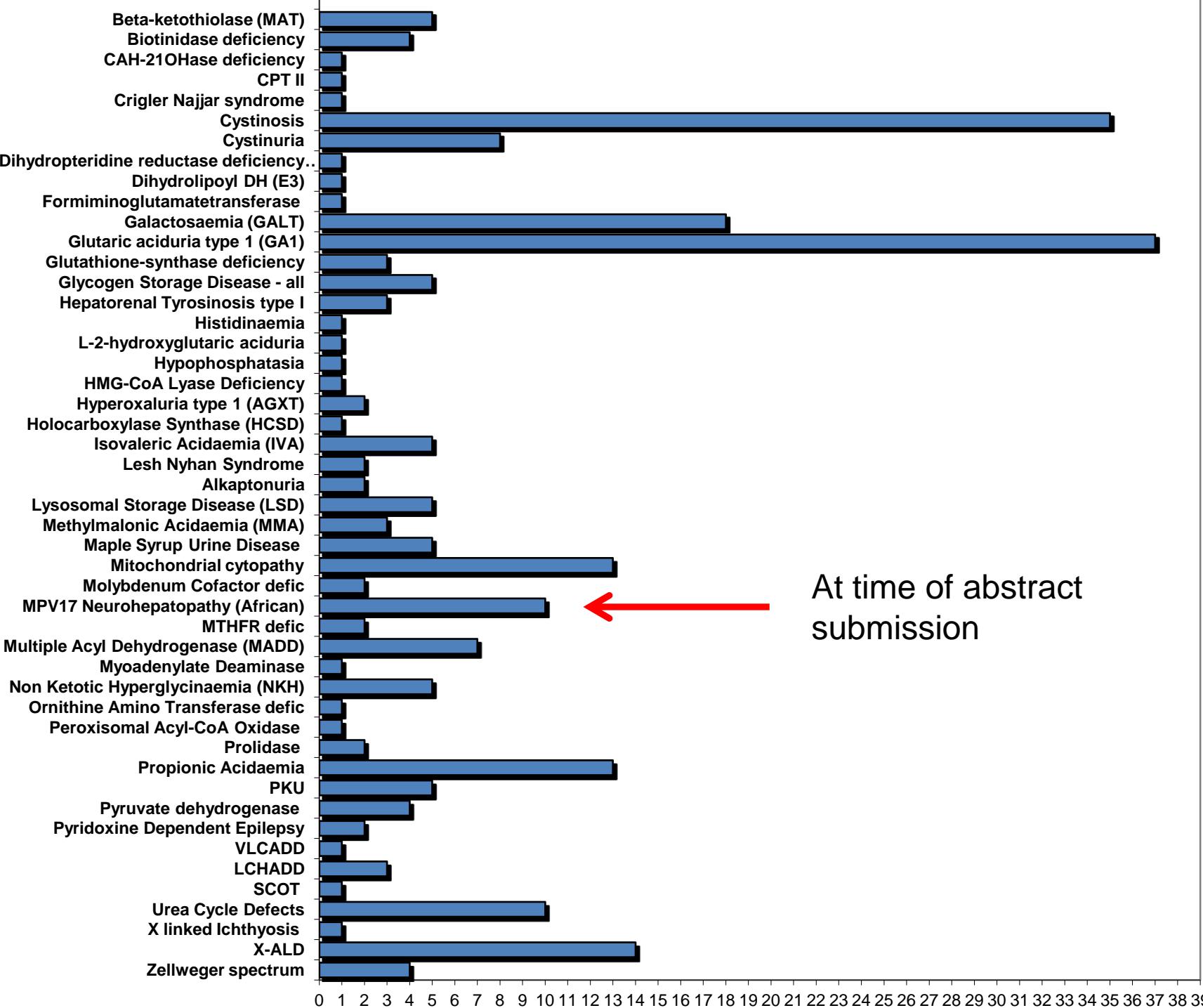
MPV17 NEUROHEPATOPATHY

(See Poster #P13)

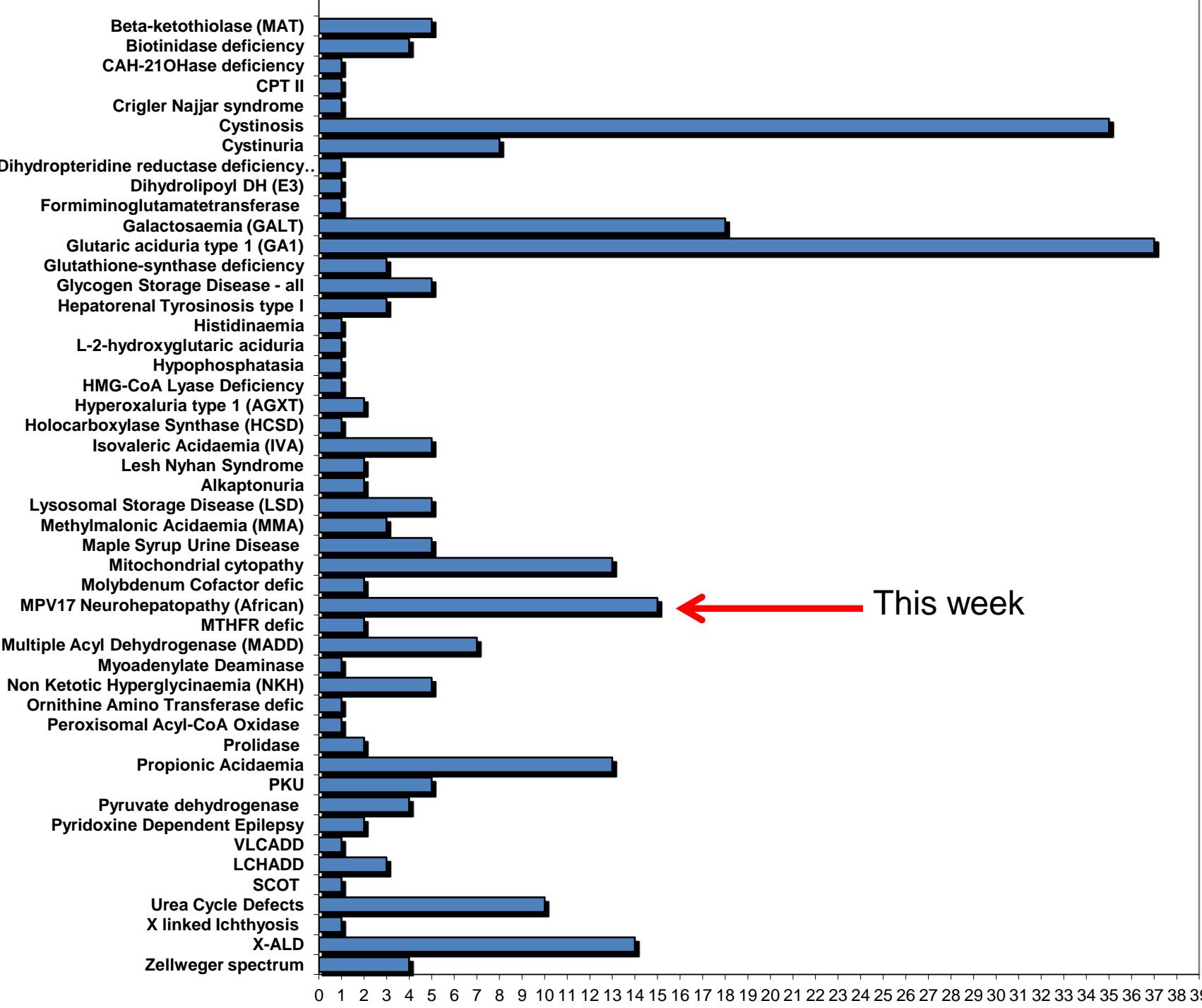


■ MPV17:p.Q36X/p.Q36X

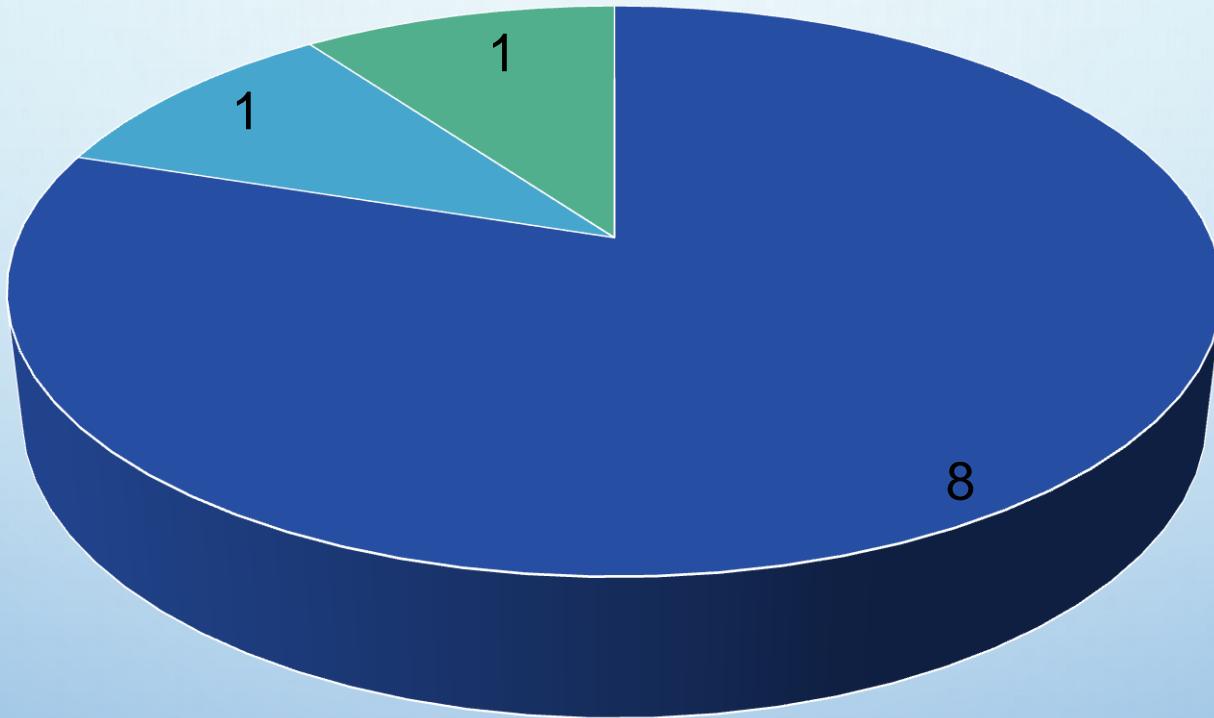
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At time of abstract
submission



PRIMARY HYPEROXALURIA (N=10)



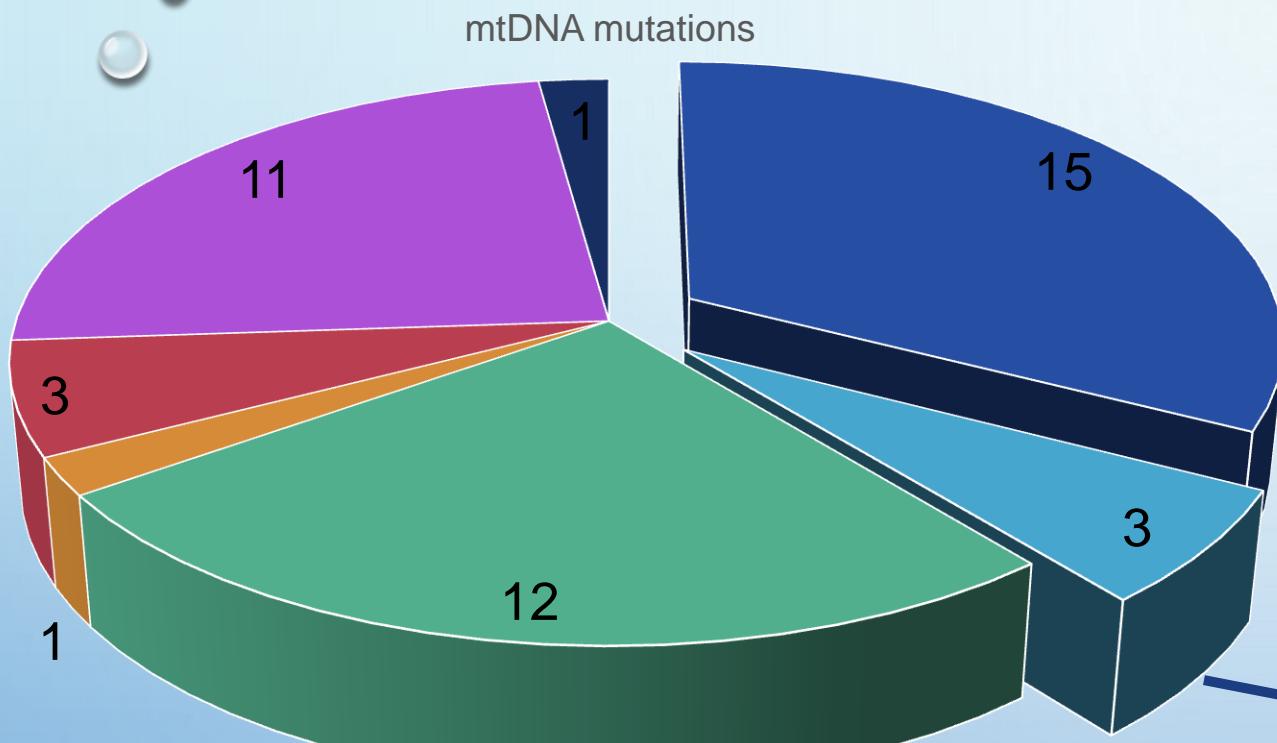
■ AGXT p.A112D/p.A112D

■ AGXT:p.A112D/p.S158L

■ AGXT c.445delG/c.445delG

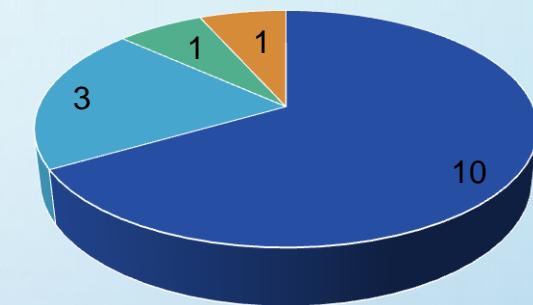
MTDNA CYTOPATHIES (N=46)

(See Poster #P14)



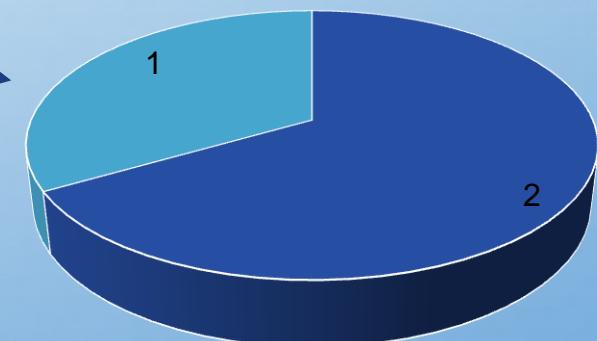
- LHON
- MELAS:m.3243A>G
- NARP/Leigh:m.8993T>C/G
- Multiple deletions
- MILS
- MERRF:m.8344
- Large mtDNA deletions

LHON mutations



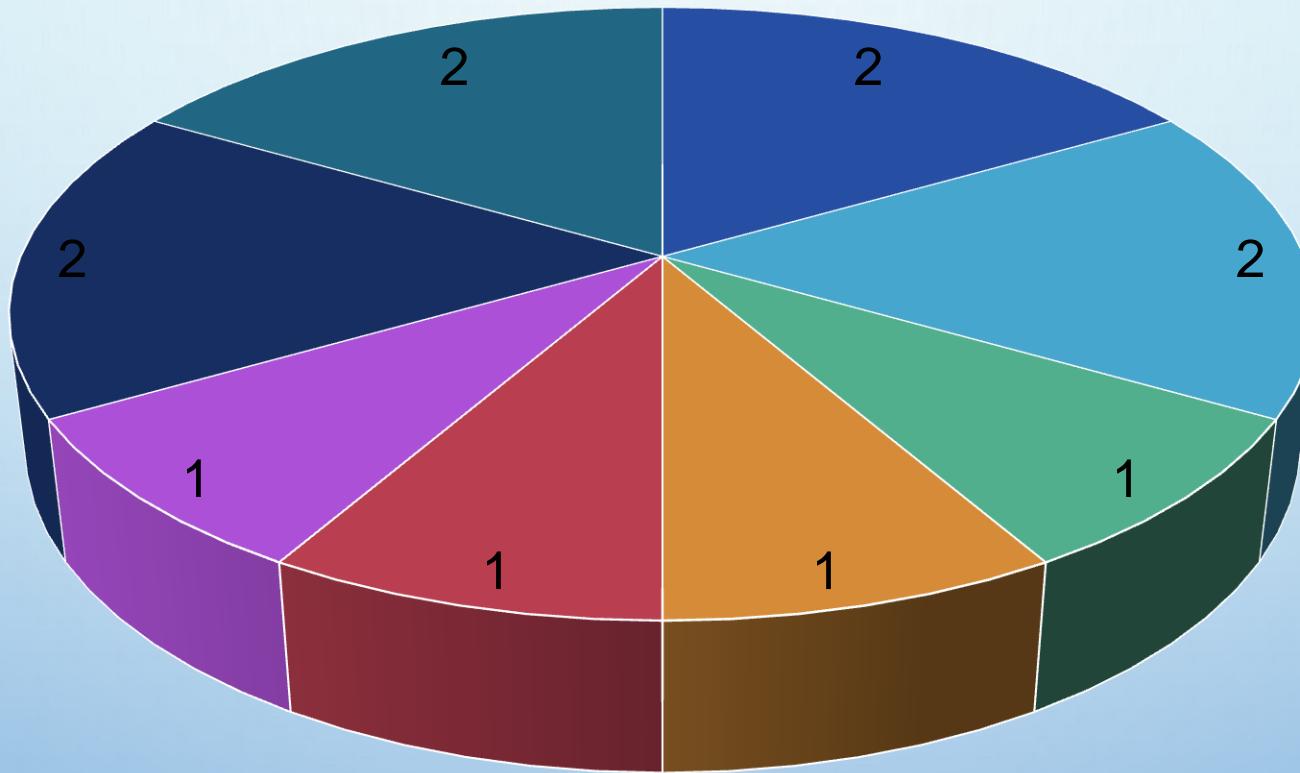
- m.11778G>A
- m.14484T>C
- m.3460G>A
- m.3635G>A

MILS mutations



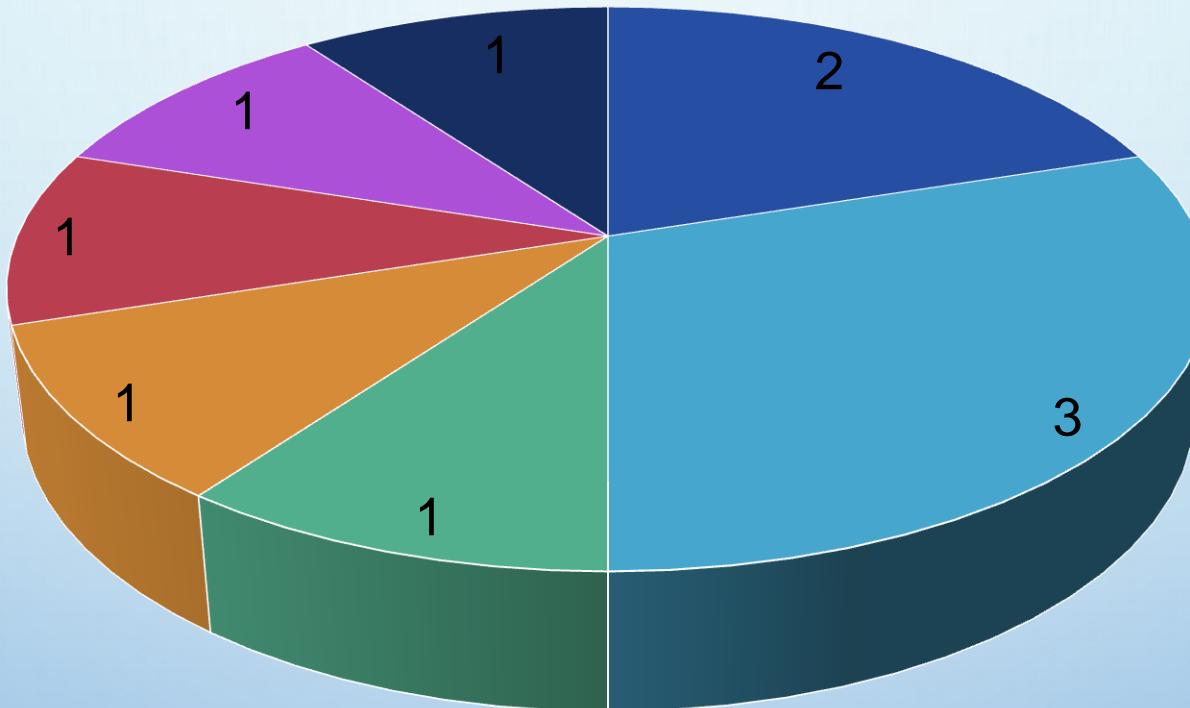
- m.14459A>G
- m.13094T>C

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

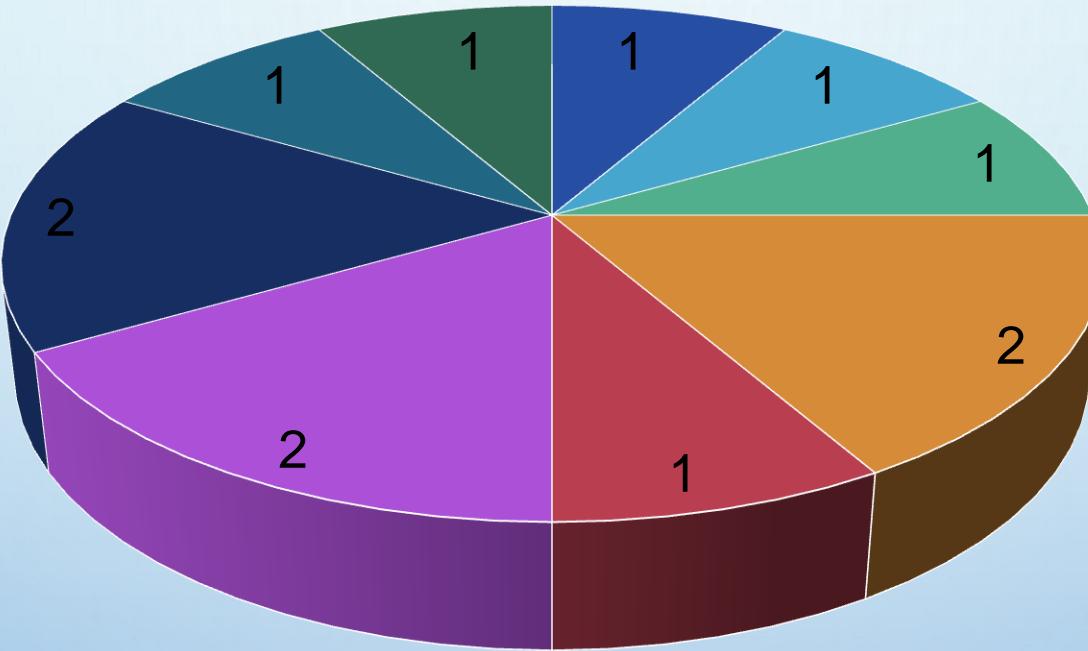
X-LINKED ADRENOLEUKODYSTROPHY (N=10)



- 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: p.Arg357Trp/conv ex 4-10
- CYP21A2: c.290-13C>G/CYP21A2*20K
- CYP21A2: p.Gln318X/Exon 6 cluster
- CYP21A2: p.R479L/?

- CYP21A2: 5` convers (incl ex 1)(?Homozyg)
- CYP21A2: c.290-13C>G homoz
- CYP21A2:p.Ile173Asn/p.Ile173Asn
- CYP21A2: conv exon 3 / conv exon 7-8

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

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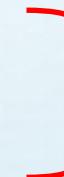
• GA1 ^[1]	p.A293T	1:36 ; 1/5 184 newborns
• Cystinosis ^[2]	c.971-12G>A	1:50 ; 1/10 000 newborns
• Galactosaemia ^[3]	p.S135L	1:60 ; 1/14 400 newborns
• MPV17 ^[4]	p.Q36X	1:68 ; 1/18 496 newborns
• PH1	p.A112D	??

- 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



Significantly amenable to treatment if diagnosed early

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.