

Homocystinuria

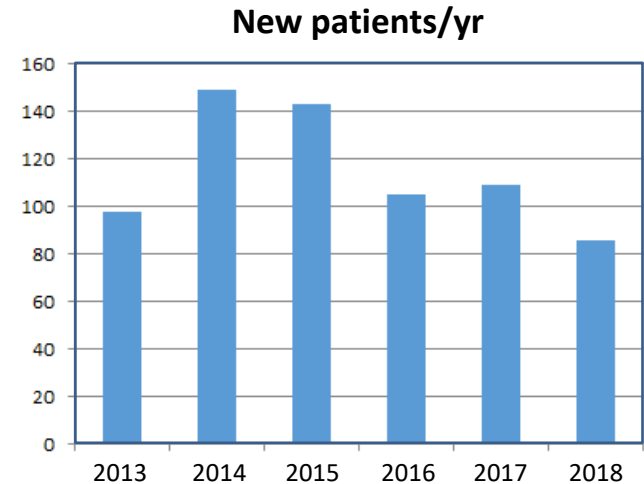
The Irish Experience

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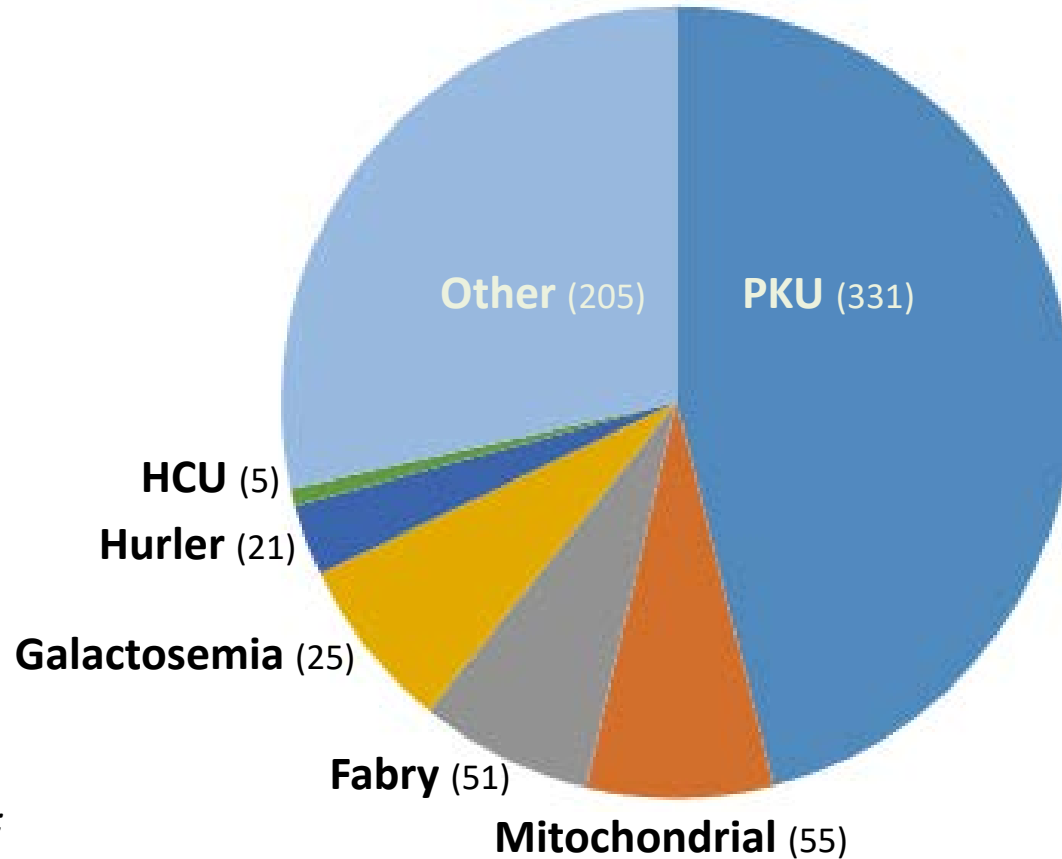
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MMUH Adult Metabolic Service

- NCIMD (CUH/TS) established in the 1960s
- Adult Unit (MMUH) set up in mid-yr 2013
- Team: 3 Consultants, 3 NCHDs, 3 Dieticians, 0.5 MSW, 0.5 Clin Psych
- Current census: 798
- No. of adults to transition: 326
- No. of patients turning 18yrs (2019-2022): 225



MMUH Adult Metabolic Service



- 50 additional adult HCU patients; anticipated transfer in 2019

The Irish Experience

- Irish incidence of pyridoxine-nonresponsive HCU ~ 1 in 65,000 ; largely due to a high prevalence of the Gly307Ser (c.919G>A) mutation in the *CBS* gene
- 1971: HCU newborn screening, using the bacterial inhibition assay
 - Blood sample obtained between 72-120 hrs of life
 - 2004: switched testing method to MS/MS
 - 2010: cut-off for Methionine levels changed from 60 to 50 $\mu\text{mol/L}$

The Irish Experience

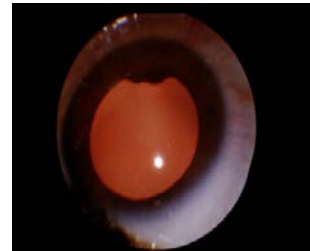
- 25-year period (1971 to 1996): 1.58 million newborn infants screened
 - 21 HCU cases identified
 - 4 HCU cases not detected, all presented clinically with ectopia lentis (age >2 yrs): 3 were breast-fed, 1 pyridoxine responsive
 - Total: 25 patients (24 pyridoxine nonresponsive)
 - No HCU-related complications in 18 screened, dietary-treated cases
 - 15 cases had lifetime medians of free homocystine ≤ 11 $\mu\text{mol/L}$ (range 4–11)
 - 3 cases had higher lifetime medians of free homocystine (18, 18 and 48 $\mu\text{mol/L}$); developed increasing myopia, an ocular feature that often precedes ectopia lentis*

The Irish Experience

Outcome following NBS

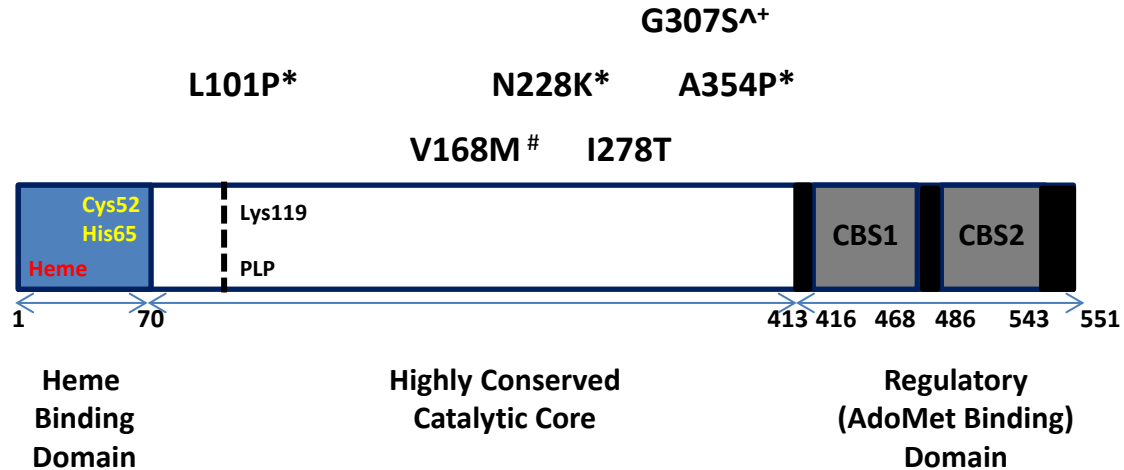
	Detected by Screening		Not detected by Screening	Born before Screening
Number	22		5	3
Complications	4		5	3
	Diet compliant	Diet poor compliance	At presentation	At presentation
Dislocated lenses	0	2	5	3
Thromboembolism	0	1	0	1
Osteopenia (X-ray)	0	1	0	0
Mental handicap	0	2	3	3

Osteoporosis



Dislocation of Lens

The Irish Experience: *CBS mutations*



⁺24/34 (71%) of alleles;
8/17 Homozygous for G307S

[^]Gu Z, et al. *Am. J. Hum. Genet.* 49: 406, 1991

⁺*Gallagher PM, et al. *Hum. Mutat.* 6: 177-180, 1995

[#]Kruger WD, et al. *Hum. Molec. Genet.* 4: 1155-1161, 1995

The Irish Experience

- 1998: Yap and Naughten observed that maintaining lifetime plasma fHcy $\leq 11 \mu\text{mol/L}$ (\sim tHcy of 100–120 mmol/L) protects against complications
 - Achieved through dietary restriction of natural protein/methionine, with methionine-free cystine supplemented synthetic AA mixtures
 - Betaine rarely used in our paediatric cohort, as dietetic compliance generally good; reserved for those with poor compliance, occasionally in late adolescence*

The Irish Experience

- Intellectual abilities assessed using age-appropriate psychometric tests (n-23 Pyr-NR individuals): *Yap S, et al. J Inherit Metab Dis. 2001*
 - 19 detected through NBS (early treated); 2 late-diagnosed; 2 untreated at the time of assessment

Patients	N	Age Mean yrs (range)	FIQ Mean (range)
HCU (NBS)	13 ⁺	14.4 (4.4-24.9)	105.8 (84-120)
HCU (PC)	6	19.9 (13.8-25.5)	80.8 (40-103)
HCU (LD)	2	18.9 / 18.8	80 / 102
HCU (UT)	2	22.4 / 11.7	52 / 53
Control group*	10	19.4 (9.7-32.9)	102 (76-116)

*lifetime plasma free homocystine median (< 11 µmol/L) had no complications

*Unaffected siblings

The Irish Experience

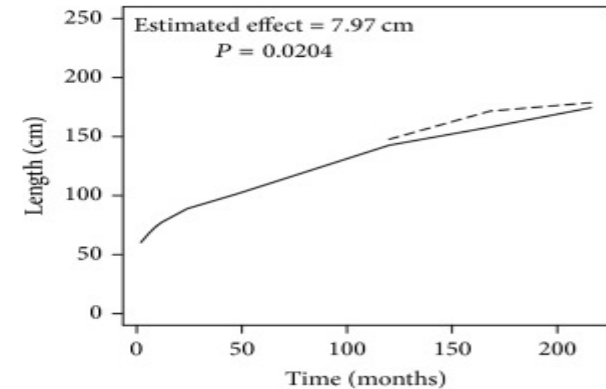
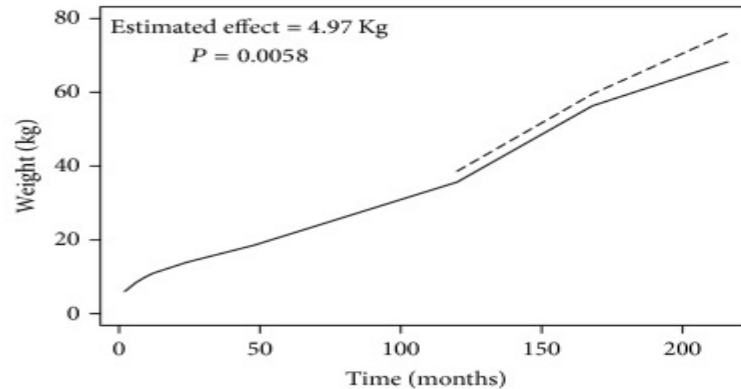
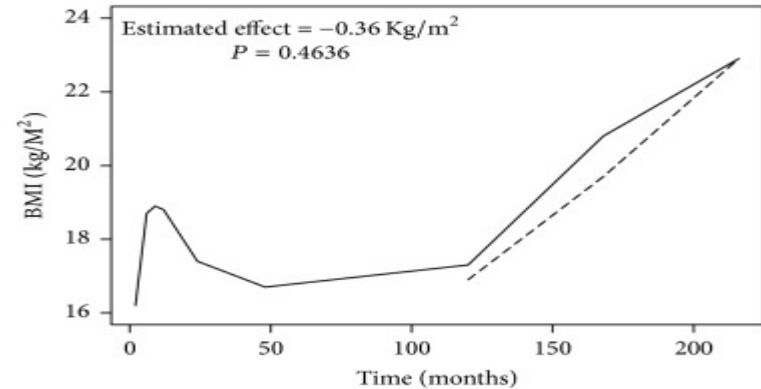
- Purcell O, et al. Growth Patterns in the Irish Pyr-NR HCU Population; Influence of Metabolic Control and Protein Intake. J Nutr Metab. 2017
- Retrospective review: N-48 HCU: 24 F, 24 M
- Up to age 18; 9 set points (*ages 3, 6, 9 and 12 mos; 2, 4, 10, 14 and 18 yrs*)

Patients	N (%)	Age at diagnosis Mean yrs (range)	Current Age Mean yrs (range)
HCU (NBS)	36 (75)	NBS	23.7 (5 mos. - 43 yrs)
HCU (LD)	12 (25)	5.09 (1.3–11.8 yrs)	34.6 (12–52.6 yrs)

Comparative growth parameters

Birth to age 18 yrs

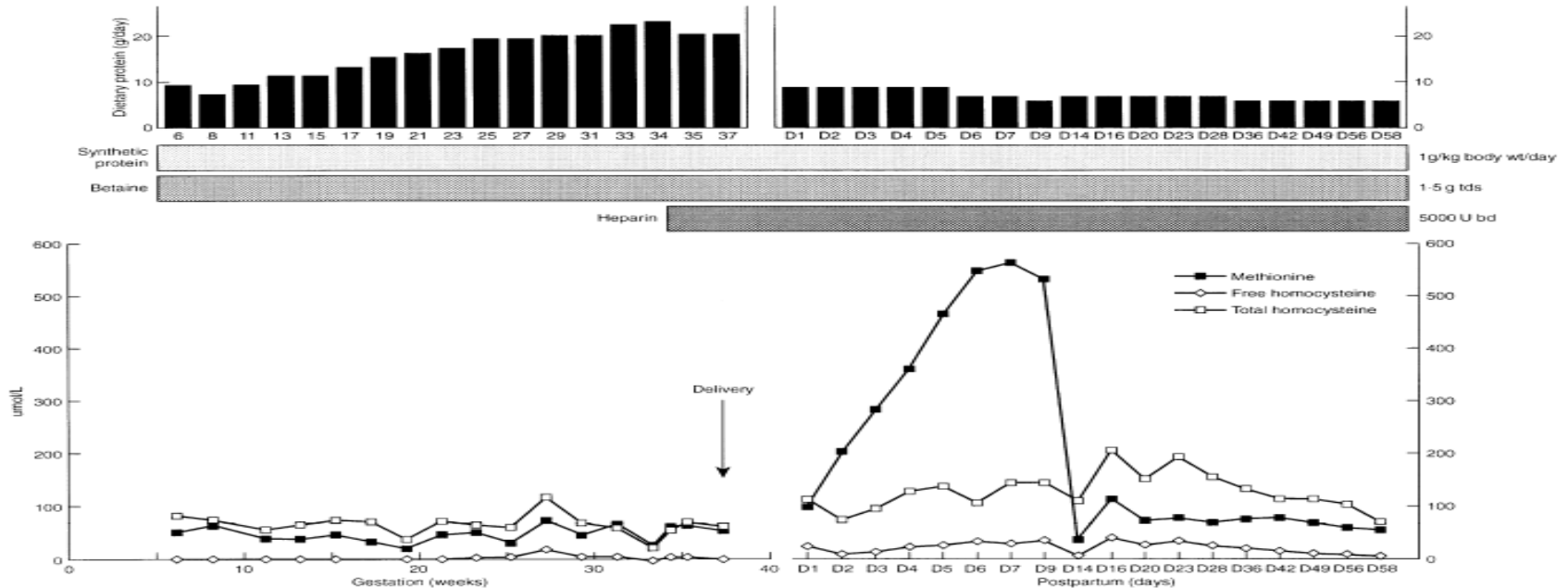
- HCU patients were heavier / taller than general population by 1 SD; although BMI similar
- Compared to NBS group (n=36), LD (12) were statistically significantly
 - Heavier (+4.79 kg)
 - Taller (7.97 cm); accelerated growth <10 yrs



--- LD group
— NBS group

The Irish Experience

- No association between intermittently low cystine levels and height
- No difference in adult height between groups with lower protein (GMDI/Ross) or higher protein intake (GOSH)



The Irish Experience

- Currently, a significant no. of adult patients are still cared for at CUH/TS
- Plan for 2019 onwards: is transition of adults patients (18yrs +1 day) to Adult Unit at MMUH
- Lab which measures homocysteine/methionine, based at CUH/TS
- Open enrolment of patients into a natural history study
- Systematic neurocognitive testing to be undertaken, with quality of life and other measures obtained