### Web Table I: Summary of Genetic Mutations, Treatment and Follow-Up in Patients with Congenital Hyperinsulinism (N=40)

| S.no | Age at onset | Gene, zygosity | Nucleotide change | Protein change | Type of variant | F-18 DOPA PET | Initial treatment | Follow-up | Development |
|------|--------------|----------------|------------------|----------------|----------------|---------------|------------------|-----------|-------------|
| P1   | Day 8        | ABCC8, Compound hetero | c.331G>A/ c.3979G>T | p.G111 R/p.E1327* | Missense/ Nonsense | Diffuse | Octreotide 35 μg/kg/day LAR started at 3 y | 9 y       | LAR 7.5 mg every 45 days | Normal, Initial motor delay |
| P2   | Day 1        | ABCC8, Compound hetero | c.1330C>T/ c.3653+2T>A | p.Q444*/p.? | Nonsense/ Aberrant splicing variant^ | Diffuse | Octreotide 40 μg/kg/day LAR 10 mg per month from 2.5 y, stopped at 3.5 y | 4.5 y     | None | Normal, Mild motor delay |
| P3   | Day 1        | ABCC8, Compound hetero | c.221G>A/ c.331G>A | p.R74Q and p.G111 R | Missense/ Missense | Diffuse | Octreotide 50 μg/kg/day; Sirolimus added but stopped due to severe anemia. Octreotide tapered and stopped at 2.5 y | 4.5 y     | None | Ht -3 SD Rest normal |
| P4   | Day 2        | ABCC8, Homo | c.522dup/ c.522dup | p.L175f s/p.L175fs | Frameshift | Diffuse | Poor response and compliance to octreotide Sirolimus 1.8 mg/m². Developed sepsis at 4 y, shifted to octreotide LAR | 4 y       | LAR 10 mg monthly | Normal, GDD, DQ 70, epilepsy on AED |
| P5   | Day 1        | ABCC8, Compound hetero | c.4480C>T/ c.(4414+1_414-1) (4749+34_?) del | p.R1494 W/p.? | Missense/ Deletion | Not done | Octreotide 40 μg/kg/day | Lost to FU after 6 mo | - | Normal, Global delay |
| P6   | Day 1        | ABCC8, Homo | c.3653+2T>G/ c.3653+2T>G | p.?/p.? | Aberrant splicing^ | Diffuse | Octreotide 40 μg/kg/day LAR 12 mg monthly since 2 y of age Sirolimus trial; stopped due to low plasma drug levels | 3.5 y     | Daily octreotide at 10 μg/kg/day LAR 12 mg monthly | Height - 3.5 SD Rest normal |
| P7   | Day 1        | ABCC8, Homo | c.2423_242 4del/ c.2423_242 4del | p.L808f s/p.L80 8fs | Frameshift^ | Diffuse | Octreotide 35 μg/kg/day LAR 10 mg monthly since 6 mo of age | 2.5 yrs | LAR 10 mg monthly | Height - 2 SD |
| P8   | Day 1        | ABCC8, Homo | c.331G>A/ c.331G>A | p.G111 R/p.G111 R | Missense | Diffuse | Octreotide 35 μg/kg/day Sirolimus tried but stopped due to deranged LFT. LAR 5 mg monthly | 2.5 yrs | LAR 10 mg q 2 monthly | Weight for height 97th centile Rest normal |

[^]: Aberrant splicing variant
[^]: Frameshift variant
[\*]: Missense change
| Day  | Mutation Details | Treatment Details | Outcome |
|------|------------------|-------------------|---------|
| **P9** | ABCC8, Homo | p.3653+2T>G/ p.?/ p.? Aberrant splicing<sup>+</sup> Diffuse Octreotide 40 μg/kg/day. Sirolimus tried but stopped due to deranged LFT. LAR 10 mg monthly started at 4 months of age. | 2 yrs LAR 10 mg monthly, Obese Wt for height 99<sup>th</sup> cent Rest normal |
| **P10** | ABCC8, Homo | c.2675_2679del/c.2675_2679del p.Q892fs/p.Q892fs Frameshift Not done Octreotide 50 μg/kg/day Planned for near-total pancreatectomy. | LAM A, expire d |
| **P11** | ABCC8, Compound hetero | c.267delT and c.619-629 del CCCGAGG ACCT p.(Ile89 MetfsTer10)/p.(Pro207AlafsTer61) Frameshift Not done Octreotide 40 μg/kg/day Expired at 4 mo due to hypoglycemia at night. | - - - |
| **P12** | ABCC8, Homo | c.1138del p.(Ala380fs)/ p.(Ala380fs) Frameshift Diffuse Octreotide 40 μg/kg/day LAR started at 5 months of age. | 1 y LAR 10 mg monthly Octreotide 10 μg/kg/day |
| **P13** | ABCC8, Compound hetero | c.331G>A/ c.441G>A p.Gly11Arg/p.Asp147Asn Missense/ Missense<sup>+</sup> Diffuse Octreotide 50 μg/kg/day LAR 5 mg monthly started at 2 mo | 4 mo Octreotide 40 μg/kg/day, LAR 5 mg monthly |
| **P14** | ABCC8, Homo | c.331G>A/ c.331G>A p.G111R/p.G111R Missense Not done Octreotide 40 μg/kg/day | 3 mo Octreotide 40 μg/kg/day |
| **P15** | ABCC8, Paternally inherited hetero | c.3871-1G>A p.?/N Aberrant splicing Diffuse Octreotide 10 μg/kg/day | 9 mo LAR 2 mg monthly |
| **P16** | ABCC8, Paternally inherited hetero | c.4024C>T/N p.Q1342fs/p.Q1342fs Missense Focal Octreotide 10 μg/kg/day | 2.5 y Off treatment since 1.2 y |
| **P17** | ABCC8, Paternally inherited hetero | c.4256G>A/N p.R1419H/N Missense Focal Octreotide 40 μg/kg/day Sirolimus 0.3 mg/m² | 1.5 y Lost to FU: Expired at 1.7 years due to sepsis Octreotide 40 μg/kg/day sirolimus Poor compliance | Normal Moderate GDD |
### Table 1: Genetic and Therapeutic Details

| Case | Age at Diagnosis | Gene | Mutation Details | Phenotype | Treatment Details | Follow-up | Outcome |
|------|------------------|------|------------------|-----------|------------------|-----------|---------|
| P18  | Day 10           | ABCC8| Paternally inherited hetero | c.1330C>T/ N | p.Q444* /N Nonsense | Not done | Octreotide 20 µg/kg/day till 2 years of age | 7 y | Off treatment since 2 years of age | Normal | Normal |
| P19  | Day 3            | ABCC8| Paternally inherited hetero | c.4415-13 G>A | p.?:/N Aberrant splicing | Focal | Octreotide 12 µg/kg/dayPartial pancreatectomy done at 7 months of age | 3 y | None | Normal | Normal |
| P20  | Day 6            | ABCC8| Paternally inherited hetero | c.331G>A/ N | p.G111 R Missense | Not done | Diazoxide | 4.5 y | 4 mg/kg | Normal | Normal |
| P21  | Day 3            | ABCC8| Hetero (de novo) | c.4377G>C/ N | p.Q1459 H Missense | No focal lesion | Diazoxide | 8 y | Stopped after 6 years | Normal | Mild MR |
| P22* | Day 1            | ABCC8| Hetero (de novo) | c.4519G>A | p.Glu1507Lys Missense | Not done | Diazoxide | 18 mo | 3.5 mg/kg | Normal | Mild GDD |
| P23  | 3 mo             | HADH | Homo | c.550A>T | p.I184F Missense | Not done | Diazoxide | 5 y | 5 mg/kg | Normal | Normal |
| P24  | 4 mo             | HADH | Homo | c.550A>T | p.I184F Missense | Not done | Diazoxide | 6.5 y | 5 mg/kg | Normal | Mild delay |
| P25  | 7 mo             | GLUD1| Hetero | c.943C>T/N | p.H315 Y Missense | Not done | Diazoxide | 4 y | 4 mg/kg | Normal | Autism |
| P26  | 6 mo             | GLUD1| Hetero | c.1334C>T/N | p.S445L Missense | Not done | Diazoxide | 7 y | 7 mg/kg, stopped at 6 yrs due to non-availability Octreotide 15 ug/day | Microcephaly | GDD, Epilepsy |
| P27  | 4 mo             | GLUD1| Hetero | c.820C>T/N | p.R274C Missense | Diffuse | Diazoxide | 10 mo | 7 mg/kg | Normal | Fine motor delay |
| P28  | 6 yrs            | None by tNGS | | | | Not done | Diazoxide | 15 y | 2 mg/kg | Obese | |
| P29  | 3 mo             | None in ABCC8/ KCNJ11 | | | | Not done | Diazoxide | Lost to follow-up at 3 y | Poor compliance | - | GDD, Epilepsy |
| P30  | 4 mo             | None in ABCC8/ KCNJ11 | | | | Not done | Diazoxide | 6 y | 0.4 mg/kg Poor compliance | Normal | GDD, poorly controlled epilepsy |
| P31  | 9 mo             | None by tNGS | | | | No focal lesion | Diazoxide | 6.5 y | 5 mg/kg | Normal | GDD, epilepsy |
| P32  | 6.5 mo           | None by tNGS | | | | Not done | Diazoxide | 5 y | 5 mg/kg | Normal | Normal |
| P33  | 3 mo             | None in ABCC8/KCNJ11 | | | | Not done | Diazoxide | Lost to FU | - | - | - |
| P34  | 5 mo             | None in ABCC8/KCNJ11 | | | | Not done | Diazoxide | Lost to FU after 3 y, Expired at 4 yrs due to | - | - | - |
| Patient | Age | Mutation Details | Status | Treatment | Duration | Dosage | Follow-up | Outcome |
|---------|-----|-----------------|--------|-----------|----------|--------|-----------|---------|
| P35     | 9 mo| None by tNGS    | -      | Not done  | Diazoxide| 5 y    | 2 mg/kg   | Normal  |
| P36     | Day 6| None by tNGS   | -      | Not done  | Diazoxide| 3 y    | 4 mg/kg   | Normal  | GDD, epilepsy |
| P37     | Day 3| None by tNGS   | -      | Not done  | Diazoxide| 2.2 y  | 2.5 mg/kg | Normal  | Mild GDD, epilepsy |
| P38     | 5 mo| None by tNGS    | -      | Not done  | Diazoxide| 1.5 y  | 10 mg/kg  | Normal  | GDD, epilepsy |
| P39     | 2 mo| KMD6A mutation causing Kabuki syndrome | ChrX:g.(?_4873552_44873987_?)del| De novo| Not done | Diazoxide, stopped due to neutropenia, Started Octreotide | Lost to FU after 1 y | Octreotide 20 ug/kg/day | Length < -2SD | GDD, epilepsy |
| P40     | 2 yr| None by tNGS    | -      | Diazoxide|          | 8 y    | 1.5 mg/kg | Normal  | Normal |

Abbreviations: Homo: homozygous; Hetero: heterozygous; tNGS: Targeted next generation sequencing; LAR: Long-acting release octreotide; FU: follow-up; LAMA: Left against medical advice; Wt: weight; Ht: height, SD: Standard deviations, AED: antiepileptic drugs; DQ: Development quotient; GDD: global developmental delay

* One affected elder sibling diagnosed at 5 years of age and having epilepsy
** Sibling of 23
^ Hyperinsulinism-hyperammonemia syndrome
* Novel pathogenic/likely pathogenic variants