Asparaginase treatment side-effects may be due to genes with homopolymeric Asn codons (Review-Hypothesis)

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Abstract. The present treatment of childhood T-cell leukemias involves the systemic administration of prokaryotic L-asparaginase (ASNase), which depletes plasma Asparagine (Asn) and inhibits protein synthesis. The mechanism of therapeutic action of ASNase is poorly understood, as are the etiologies of the side-effects incurred by treatment. Protein expression from genes bearing Asn homopolymeric coding regions (N-hCR) may be particularly susceptible to Asn level fluctuation. In mammals, N-hCR are rare, short and conserved. In humans, misfunctions of genes encoding N-hCR are associated with a cluster of disorders that mimic ASNase therapy side-effects which include impaired glycemic control, dislipidemia, pancreatitis, compromised vascular integrity, and neurological dysfunction. This paper proposes that dysregulation of Asn homeostasis, potentially even by ASNase produced by the microbiome, may contribute to several clinically important syndromes by altering expression of N-hCR-bearing genes. By altering amino acid abundance and modulating ribosome translocation rates at codon repeats, the microbiomic environment may contribute to genome decoding and to shaping the proteome. We suggest that impaired translation at poly Asn codons elevates diabetes risk and severity.

1. Foundation of the hypothesis

Core hypothesis: translocation rates, poly Asparagine (Asn); insulin-receptor-substrate 2 (IRS2) and diabetes; hypothesis tests, poly glutamine (Gln) HTT and ataxias. Despite similar Asn codon usage, ~4%/gene, from plants to humans (1), mammals are distinguished by a paucity of genes with a long Asn homopolymeric coding region (N-hCR) (2). The 17 human genes with the longest N-hCR (ranging from five to eight consecutive Asn codons) are listed in Fig. 1; Table I lists genes with N-hCR greater than three. IRS2, encoding an insulin signal transducer, is the gene at the top of the list in Fig. 1 and multiple disorders of energy homeostasis and the urea cycle are associated with genes in Table I. The central hypothesis of this paper is that manifestations of these disorders may partly be attributable to reduced plasma Asn concentrations, which in turn may disproportionately affect the production of proteins containing N-hCR. More broadly, we propose a model in which protein expression may be affected at amino acid homopolymeric coding regions (hCR) in general because translation elongation rates at hCR could reflect variation in the levels of the corresponding amino acids. This model may contribute to explaining an association, initially noted with poly Gln codon runs, between hCR and some human diseases (1,3).

Asparaginase (ASNase) is a component of highly effective chemotherapeutic regimens used to treat pediatric acute lymphoblastic leukemia (ALL) (4,5) and some lymphomas (6-8). ASNase treatment has been estimated to have contributed to the sparing of the lives of upwards of 60,000 children in the US in the decades following its discovery (9) and rapid introduction to the clinic (10). However, ASNase treatment is not without hazard; it can produce a myriad of side-effects that include hyperglycemia, dislipidemia, pancreatitis, vascular accidents and adverse neurological outcomes. The physiological mode of action of ASNase is unclear. The enzyme deaminates Asn and Gln with production of altered amino acid ratios and ammonia (11-15). ASNase inhibits synthesis of proteins in vitro (16) and in vivo (17,18) by a mechanism consistent with reduced ribosomal translocation at Asn codons. In humans, ASNase treatment protocols cause depletion of plasma Asn and modest reductions of plasma Gln levels accompanied by mild transient hyperglycemia and occasional ketoacidosis (11,19,20). In mice, administration of ASNase causes Asn depletion in plasma and some tissues, e.g., skeletal muscle (21,22), indicating, importantly, that intracellular Asn

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can also be depleted. Moreover, in mice, impaired glucose tolerance following ASNase treatment can be improved by amino acid supplements which serve to moderate amino acid ratio imbalances (23) and Asn administered directly to mice reverses adverse events initiated by ASNase (24). In rabbits, ASNase induces dose-dependent glycemic dysregulation extending from transient mild glycosuria to hyperglycemia and diabetes (25,26). Prednisolone has been shown to potentiate the action of ASNase: both drugs can cause hyperglycemia when used alone; but predisolone synergizes with ASNase to cause

![Figure 1. Asn homopolymeric coding regions (N-hCR)-bearing-genes from 8N-hCR to 5N-hCR. The 17 human genes with N-hCR of length greater than five. Human genes are grouped by N-hCR length. Rows list genes, labelled on the left and grouped by N-hCR length in descending order from insulin-receptor-substrate 2 (IRS2) with 8N-hCR. Columns of colored panels suggest (manually annotated) functional categories: purple, diabetes and metabolism; yellow, membrane and mitochondria; blue, neuro; pink, cancer and immunity; grey, cardiovascular, blood and bone; green, DNA/RNA. Karlin et al (1) have speculated that N-hCR shorter than five in length would arise by chance. However, Kriel and Kriel (2) demonstrates that the statistical difference between mammals and nonmammals continues to hold at least down to 3N-hCR. The cutoff threshold of significance would then reduce to 2N-hCR, and to the definition of a transcription unit, cf. VEZF1, which has multiple cDNAs defining infrequently used exons. N.B. Adjacent, potentially cojoined (380) genes are used to categorize PAPPA-AS1 and ALS2CR11. Like the PAPPA locus, the MEPC2 locus also has an N-hCR bearing antisense transcript, with a 7N-hCR (AF361491); The metabolic disease and retinal development associated gene SIX3 has an antisense transcript in human SIX3-AS1 (NR_1037686.1) and mouse SIX3-OS1 (NR_038083.1). SNP rs16882396 marks the association of periodontal disease with TMEM178B. The 49 genes with 4N-hCR are: ACACA, ACACB, AGBL2, BAII, BMP2, C2orf61, CD9, CFR, CHRM2, CNIT10, EOMES, EPPIN, EPPIN-WFDC6, EVI2A, FAM193A, FRS3, GTF2I, I9R, KIAA1841, KIF3C, KLF17, LEMD3, LRPD6, MAM12, MYRF, NCOA1, PAPR3, PEAK1, PPPIR3B, RNF103, SH3D19, SI, SLIT1, SLIT2, SLIT3, SNAP91, TAB2, TAB3, TAXIBP1, TEC, TMEM65, TTX3, TRPM6, TRPM7, TTR, TTYL5, UBE4A, ZDAX, ZDB; Unorthodox human proteins deserving closer attention are from unusual cDNAs: Map3K2 4N-hCR AAH65755.1; TCR 5N-hCR AIE11180.1; Vκ 5N-hCR AAO11865; and Vλ 4N-hCR AAD29331.1. The germline V regions of immunoglobulin (Ig) as well as T cell receptor AlphaJ regions are represented in Table I as 3N-hCR. However, there are rearranged cDNAs encoding for up to 5N-hCR in some hypervariable regions (HVR) that do not appear in the germline N-hCR (used for assigning length of N-hCR when classifying these genes). It is unclear what benefits, if any, could accrue to an Ig synthesized and, potentially, folded at a rate regulated by Asn levels at N-hCR. An arbitrary list of genes that may respond to fluctuations in other amino acids include: CNDP1, CYP21A2, SELT, SELM (L-hCR); CACNAID (M-hCR); HSD11B1 (Y-hCR); NR4A3 (H-hCR); TAF9, URI1, ASPN, EFTUD2, GLTSCR1, THBS4 (D-hCR); HRC (D-, E-, H-hCR); ATAD2 (S-, D-hCR); EIF5B (K-, D-, E-hCR); KCNMA1, MAP3K1, CXCR4, WDR26, YNCR1, SRRM2 (S-, T-, G-hCR); CACNA1A (H, N, Q-hCR); POU4F2 (M-, G-, H-, S-hCR); POU3F2 (G-, H-, Q-hCR); SKD1AI (H-, E-, A-hCR); USP54 (H-, N-hCR); ATXN1, ATXN2, ATXN3, ATXN7, AR, KMT2D, KMT2C, MAMC2, MAML3, FOXO2, ARID1A, ARID1B, ARID2B MED12, MED15, NCOA3, NCOA6, IRF2BPL, VEZF1, ABCF1 and HTT (Q-hCR). The HCR appear in proteins from the NCBI homologene (381) database.

### Figure 1.

Asn homopolymeric coding regions (N-hCR)-bearing-genes from 8N-hCR to 5N-hCR. The 17 human genes with N-hCR of length greater than five. Human genes are grouped by N-hCR length. Rows list genes, labelled on the left and grouped by N-hCR length in descending order from insulin-receptor-substrate 2 (IRS2) with 8N-hCR. Columns of colored panels suggest (manually annotated) functional categories: purple, diabetes and metabolism; yellow, membrane and mitochondria; blue, neuro; pink, cancer and immunity; grey, cardiovascular, blood and bone; green, DNA/RNA. Karlin et al (1) have speculated that N-hCR shorter than five in length would arise by chance. However, Kriel and Kriel (2) demonstrates that the statistical difference between mammals and nonmammals continues to hold at least down to 3N-hCR. The cutoff threshold of significance would then reduce to 2N-hCR, and to the definition of a transcription unit, cf. VEZF1, which has multiple cDNAs defining infrequently used exons. N.B. Adjacent, potentially cojoined (380) genes are used to categorize PAPPA-AS1 and ALS2CR11. Like the PAPPA locus, the MEPC2 locus also has an N-hCR bearing antisense transcript, with a 7N-hCR (AF361491); The metabolic disease and retinal development associated gene SIX3 has an antisense transcript in human SIX3-AS1 (NR_1037686.1) and mouse SIX3-OS1 (NR_038083.1). SNP rs16882396 marks the association of periodontal disease with TMEM178B. The 49 genes with 4N-hCR are: ACACA, ACACB, AGBL2, BAII, BMP2, C2orf61, CD9, CFR, CHRM2, CNIT10, EOMES, EPPIN, EPPIN-WFDC6, EVI2A, FAM193A, FRS3, GTF2I, I9R, KIAA1841, KIF3C, KLF17, LEMD3, LRPD6, MAM12, MYRF, NCOA1, PAPR3, PEAK1, PPPIR3B, RNF103, SH3D19, SI, SLIT1, SLIT2, SLIT3, SNAP91, TAB2, TAB3, TAXIBP1, TEC, TMEM65, TTX3, TRPM6, TRPM7, TTR, TTYL5, UBE4A, ZDAX, ZDB; Unorthodox human proteins deserving closer attention are from unusual cDNAs: Map3K2 4N-hCR AAH65755.1; TCR 5N-hCR AIE11180.1; Vκ 5N-hCR AAO11865; and Vλ 4N-hCR AAD29331.1. The germline V regions of immunoglobulin (Ig) as well as T cell receptor AlphaJ regions are represented in Table I as 3N-hCR. However, there are rearranged cDNAs encoding for up to 5N-hCR in some hypervariable regions (HVR) that do not appear in the germline N-hCR (used for assigning length of N-hCR when classifying these genes). It is unclear what benefits, if any, could accrue to an Ig synthesized and, potentially, folded at a rate regulated by Asn levels at N-hCR. An arbitrary list of genes that may respond to fluctuations in other amino acids include: CNDP1, CYP21A2, SELT, SELM (L-hCR); CACNAID (M-hCR); HSD11B1 (Y-hCR); NR4A3 (H-hCR); TAF9, URI1, ASPN, EFTUD2, GLTSCR1, THBS4 (D-hCR); HRC (D-, E-, H-hCR); ATAD2 (S-, D-hCR); EIF5B (K-, D-, E-hCR); KCNMA1, MAP3K1, CXCR4, WDR26, YNCR1, SRRM2 (S-, T-, G-hCR); CACNA1A (H, N, Q-hCR); POU4F2 (M-, G-, H-, S-hCR); POU3F2 (G-, H-, Q-hCR); SKD1AI (H-, E-, A-hCR); USP54 (H-, N-hCR); ATXN1, ATXN2, ATXN3, ATXN7, AR, KMT2D, KMT2C, MAMC2, MAML3, FOXO2, ARID1A, ARID1B, ARID2B MED12, MED15, NCOA3, NCOA6, IRF2BPL, VEZF1, ABCF1 and HTT (Q-hCR). The HCR appear in proteins from the NCBI homologene (381) database.
disruption of insulin signaling due to deletion of I-S2 (92). TXNIP also affects pancreatic β-cell biology (93), for translational sensitivity to Asn concentration, other genes with N-hCR could be tested, including conserved genes with other parameter (such as inflammatory response profiles) (87). For example an exceptional mammalian gene, with an N-hCR the largest of all proteins by ribosomal synthesis. By contrast, γ-amino butyric acid (GABA) levels are 10-fold more negatively correlated with fasting insulin levels. In the Framingham data, the maximal negative correlation observed between Asn concentration and fasting insulin also extends to additional diabetes metrics such as body mass index (BMI), waist circumference (WC), homeostatic model assessment (HOMA), and triglyceride levels. In a third study, of a different cohort, Asn was the amino acid most negatively correlated with adiponectin, HOMA and leptin levels (29). Because therapeutic Asn depletion induces glycemic dysregulation, low Asn levels may not merely be correlative associated with poor glycemic control, but may be causative or provocative. This raises the question of the potential mechanisms by which Asn depletion in plasma or tissues could adversely impact glucose homeostasis.

The possibility that N-hCR can be implicated in the etiologies of some diabetic syndromes is supported by the enrichment of genes governing metabolic balance among the list of those containing N-hCR. Approximately one-fifth of the genes bearing N-hCR in Table I are associated with metabolic disorders, obesity, diabetes, urea cycle or pancreatic islet β-cell regulation. Among these, IRS2 is of particular note. IRS2 encodes insulin receptor substrate-2, a labile (30,31) intracellular signal transducer that is a substrate for a number of membrane spanning receptor tyrosine kinases specific for extracellular cytokines that include insulin, insulin-like-growth-factor-1, erythropoietin, thrombopoietin, growth hormone, leukemia inhibitory factor, interleukin-4 (IL-4) and interferon-γ (32-37). Sequence polymorphisms in the human IRS2 locus have been associated with obesity (38), type 2-diabetes-mellitus (T2DM) (39,40) or its complications (41,42), aspects of schizophrenia (43) and IgE immune responses (44). In transgenic mice, IRS2 depletion causes compromised maintenance of β-cell mass and produces a diabetic state similar to T2DM (45,46). Reduced levels of IRS2 in humans have been proposed to lead to desensitized insulin/cytokine signalling and thus to hyperglycemia/mutated immune responses, with prolonged IRS2 deficits exacerbating islet cell mass reduction leading to T2DM (47-50). Alterations in IRS2 expression have been associated with altered lipid metabolism in obese subjects (51) and have been correlated with development of insulin nonresponsiveness in obese boys (52). IRS2 has eight consecutive Asn-codons located 19 codons after initiation AUG codon. Depletion of the levels of the cognate Asn aminoacyl-tRNA may result in compromised elongation in the homopolymeric Asn coding region that may be especially deleterious to the synthesis of IRS2 due to the location of the N-hCR.

Codon usage and ribosome translocation rates affect protein expression in bacterial (53-57), viral (58,59) and human genes (60,61). Ribosomal footprinting studies have suggested that the stability of translation initiation complexes increases when nascent chains emerge from the exit tunnel or folding vestibule to engage chaperones (62). Ribosomal stalling may potentially lead to translation termination when the elongation rate is diminished in the ‘translation-initiation-ramp’ or instability region (63-65). The concept of the ramp, which may not apply to all mammalian genes, remains controversial (66) and though potentially contributory, it is not essential to the overall thesis proposed here. In general, a severely diminished elongation rate may lead to premature termination; for example in prokaryotes, ribosomal stalling induces a translational termination mechanism through tmRNA (67, 68). In the abstract, reduced rates of translation anywhere along an mRNA would result directly in a reduced overall rate of target protein synthesis and, depending on protein half-life, result indirectly in decreased steady state levels of such proteins. High rates of translation may even increase the half-life of an mRNA (69).

Of the genes that have been identified with N-hCR of length 3 or greater, approximately one third can be associated with cancer and immune response, one quarter with neuro-degeneration (20% with metabolic disorders, above), and eight percent with vasculature and hematopoiesis. Of the remaining ~14%, many can be classified as involved with chromatin modification, DNA maintenance and repair, RNA transcription and processing or protein synthesis and turnover, some have Leucine rich repeats that can serve as pattern recognition elements. Some genes fall into multiple categories, e.g. IRS2 is associated not only with diabetes and receptor mediated signal transduction for specific extracellular cytokines, but also with epilepsy (70), aspects of schizophrenia (43), Alzheimer’s disease (71-73), retinal degeneration (74), hippocampal synaptic plasticity (75), long term potentiation of hippocampal synaptic transmission (76), ataxia (77), cardiac failure (78), kidney development (79), renal disease (80), breast cancer (81,82), rhabdomyosarcoma (83) and, in conjunction with JAK2(N-ACR), hematopoiesis (84,85). A limited study of an N-hCR length polymorphism in IRS2 shows no association with diabetes (86).

For the purpose of establishing the consequences of N-hCR for translational sensitivity to Asn concentration, other genes with N-hCR could be tested, including conserved genes with nonhuman N-hCR lengths that also differ from humans in some other parameter (such as inflammatory response profiles) (87). For example an exceptional mammalian gene, with an N-hCR longer than the 8N-hCR of IRS2, is a bat paralog of the IL8-receptor, CXCR2, (EPQ18419), which has a 60N-hCR. Other genes of interest from mouse, that differ from human in N-hCR length, include MDR1 and CFTR (a Salmonella receptor), and TNFRSF16/BEX3A/NGFRAP1 (implicated in diabetes) (88) as well as the redox regulators: GCLC (89) and TXNIP (90) (the former encodes the first, rate limiting, enzyme in the glutathione synthesis pathway and has been associated with cardiovascular events) (91); the latter encodes a conserved thioredoxin binding protein that has an 8N-hCR in mice, vs. a 3N-hCR in nonrodent mammals. All of these TXNIP N-hCR are invariantly located and they begin at codon 386, end 3 codons before the stop codon. This is discussed further, below, along with the contribution of TXNIP to host response to P. aeruginosa bacteremia by recruitment of neutrophils in mice (92). TXNIP also affects pancreatic β-cell biology (93),
| A2M       | ATP6V1C1 | CES2 | DNAH1 | FSP1 | KHDRBS2 | LY75 |
| AATK      | BAG5     | CFAP45 | DNAH6 | FSTL3 | KIAA0232 | LYST |
| ACACA     | BAG6     | CFAP54 | DNAJB1I | G3BP1 | KIAA1024L | MALT1 |
| ACACR     | BAI2     | CFTR  | DNAL4 | GABBR1 | KIAA1107 | MAML2 |
| ACAN      | BCAS1    | CGRFF1 | DNMTL1 | GBP6  | KIAA1210 | MAP7 |
| ACDBG2    | BCAS3    | CHAD  | DNMT3A | GCLC  | KIAA1217 | MAPK8P2 |
| ADAM10    | BIN2     | CHD7   | DNTT1P2 | GDPD1 | KIAA1549L | MPR22 |
| ADAM19    | BIRC6    | CHE2K | DOCK4  | GGA1   | KIAA1586 | MARC1 |
| ADAM30    | BMP2R    | CHFR   | DRD1   | GGA3   | KIAA1671 | MARCHE |
| ADCY8     | BNIPS1   | CHRM2  | DSCAM  | GIN1   | KIAA1841 | MAS1 |
| ADCY9     | BOC      | CHRM3  | DSPH   | GIT2   | KIDINS220 | MBD5 |
| AERP1     | BODL1I   | CHRN3  | DUSP10 | GJ9    | KIF16B  | MDG2 |
| AFF2      | BRPI1    | CHRM5  | DUSP21 | GK     | KIF1A   | MEDI |
| AGAP1     | BRCAR2   | CHSY1  | DYNC1H  | GKN1  | KIF21A  | MEX3B |
| AGB2      | BTA1     | CKAP2L | DYNC11I | GNZ    | KIF5C   | MGAM |
| AKAP4     | BTBD1    | CLCA1  | DYNC112 | GNPT  | KLFL17  | MGAM2 |
| ALDH6A1   | BTBD2    | CLCA2  | DYSK   | GOLPH3 | KHLH3   | MGAT2 |
| ALKBH8    | BTBD3    | CLCA3P | DZIP1  | GP1BA  | KHLH30  | MBI1 |
| ALPK2     | BTG4     | CLCA4  | ECM2   | GPATCH2 | KMT2A | MID1 |
| ALS2CR11  | C1sorf63 | CLEC10A | EFNB2  | GPR112 | KMT2E | MIS18BP1 |
| AMBRA1    | C1orf86  | CLEC6A | EIF2A  | GPR126 | KNG1 | MITF |
| AMY2A     | C1QB     | CLMN   | ELAVL2 | GPR64 | [101006032] | MLLT3 |
| AMY2B     | C1QL2    | CLTC   | ELF1   | GPR82 | [101006038] | MNO2 |
| ANAPC7    | C1QL3    | CNOT30 | EOMES  | GSG2  | [102723859] | MBTP |
| ANK3      | C2orf49  | CNOT2  | EPCAM  | GTF2I | [102723846] | MTC1 |
| ANK5      | C2orf61  | CNOT6  | EPPIN  | HAC1L | [102725117] | MTERF1 |
| ANKFN1    | C5orf67  | CNOT6L | EPPIN-WFDC6 | HAVCR1 | LAMA3 | MTG2 |
| ANKFY1    | C7       | CNST   | ERPS   | HCF2  | LAMB4 | MTRN1A |
| ANKRD17   | C5orf67  | COBL   | EPRC   | HECTD4 | LAMC2 | MTTU |
| ANKRD28   | C5orf67  | COBLL1 | ERYA   | HERC6 | LAMP2 | MUP2 |
| ANKRD44   | C7       | CPEB4  | EYA1   | HERUDP1 | LARP4 | MUC19 |
| ANKRD7    | C5orf67  | CPM    | F5     | HERUDP2 | LEMD3 | MUC3A |
| ANPEP     | CACNA1A  | CPNE9  | FAM117B | HLA-DPA1 | LGLI | MUC4 |
| ANTRX1    | CACNA1C  | CPS1   | FAM12A  | HLTF  | LGL3 | MXRA5 |
| ANTRX1L   | CACNA1D  | CPX2M  | FAM17B | HMCN1 | LGN6 | MOY10 |
| AP2B1     | CACNA1F  | COX9    | FAM193A | HNRNPL | LIMS2 | M vents |
| AP4E1     | CACNA1H  | CPEB4  | FAM208B | HNRNPUL1 | LINGO2 | M vents |
| APB2A     | CACNA1S  | CPM    | FAM65B | HRG | LITAF | MOY1B |
| APC       | CALHM1   | CPNE9  | FAM69C | HSD3B1 | LPHN2 | MOY1E |
| APCDD1    | CARF     | CPS1   | FANC1  | HSP2 | LRFN2 | MOY1F |
| AP0B      | CASC5    | CPX2M  | FAT2   | HYMP | LRFN5 | MOY6 |
| APOL1     | CASS4    | CRTAC1 | FAT3   | ICE1 | LRG1 | MOY9A |
| APK5      | CASZ1    | CSM2D | FAT4   | IGDCC3 | LRG2 | MOY9B |
| ARHGAP11A | CATSPERD | CSTF3  | FBXL5 | IGLTEL5-54 | LRG3 | MOY11 |
| ARHGAP20  | CCD144A  | CUL1   | FBX027 | IL1RAP | M7RPB | MTF1 |
| ARHGAP24  | CCD144NL | CUL3   | FBX037 | IL23R | M7RP2 | NBP1 |
| ARHGEF10  | CCD18    | CXC12  | FBX038 | IL6R  | M7RP4 | NBP4 |
| ARHGEF5   | CCD36    | CXC1L2 | FBX039 | ING3 | LRP5 | NBP5 |
| ARHGEF6   | CCD36    | CYP19A1 | FBX049 | INTS12 | LRP6 | NBR1 |
| ARID1A     | CCD37   | CYSLTR2 | FBX05  | IPA4 | LRPPRC | NCM2 |
| ARID1B     | CCD38A   | DCAF6  | FBX07  | IPRM | LRPC3 | NCPAH2 |
| ARID5B     | CCKAR    | DCAF7  | FCGR2A | IRAK3 | LRBC37A | NCPAP1 |
| ARM3C      | CCNT1    | DCBLD1 | FCGR2B | IRS2 | LRBC37A | NCOA1 |
| ARM4C      | CD63     | DCN   | FCGR2C | ISL2R | LRBC37A3 | NCOA3 |
| ARPP21     | CD9      | DDAS1  | FCN1   | ITGAV | LRBC38 | ND4 |
| ASB2       | CDC14A   | DDAS2  | FCRL4  | ITGB1BP1 | LRCC8 | NCA3 |
| ASCL5     | CDH9     | DDX4  | FEZ1   | ITK | LRCC8 | ND4 |
| ASIC2      | CDHR1    | DDX42 | FGB    | JAK2 | LRCC7 | NDC1 |
| ASPN       | CCK5     | DDX59  | FKBP7  | JMD1C | LRCC71 | NEAT1 |
| ATAD5      | CDON     | DHX38  | FLJ1   | KNCY | LRCC72 | NFLY1 |
| ATF7IP     | CEACAM5  | DIAPH1 | FLRT1  | KCNA3 | LRCC8 | NIPAP2 |
| ATFI7P2    | CELS3    | DIDO1  | FLRT3  | KCNH4 | LRCC8B | NK2Z-5 |
| AT2L       | CEMIP    | DGLAP5 | FNDC4  | KCNH8 | LRRN1 | NNT |
| ATP2B1     | CENPC    | DMD   | FNDC5  | KDM3A | LRNR2 | NOD1 |
| ATP2B3     | CEP350   | DXL2 | FNS3  | KDM6A | LRTOMT | NOD2 |
| ATP2B4     | CERS2    | DMKN | FSHR  | KDM6B | LTF | NOS2 |
Table I. Continued.

| Gene   | Description                  | Description                  | Description                  |
|--------|------------------------------|------------------------------|------------------------------|
| NOTCH1 | PKDREJ | RHDI10 | SLC2A12 | SUSD1 | TEMEM259 | UTY  |
| NPNT   | PKD1L3 | REG4   | SLC35A4 | SUZ12 | TMOND1  | VEPH1|
| NPY1R  | PKHD1L1 | RELA | SLC6A1 | SYCP1 | TRPMS11A | VEZF1|
| NPY6R  | PKP1   | RGL1   | SLC6A4 | SYNP2 | TRPMS11D | VGLL4|
| NR1D1  | PLEKHG3 | RLF  | SLC6A8 | TAB2  | TRPMS15 | VNR2 |
| NPK    | PLS1   | RM1    | SLCO3A1 | TAB3  | TNRCE6A | VPS13A|
| NRP1   | PMS1   | RNF103 | SLT1  | TALPD3 | TNRC6B | VPS4A|
| NSUN7  | PNLIPRP1 | RNF128 | SLT2  | TANGO2 | TOX3 | VPS45 |
| NTSE   | POZG   | RNF139 | SLT3  | TA52R8 | TPGS1 | WDR13 |
| NTRK3  | PPAP2B | RNF157 | SLTRK1 | TAX1BP1 | TRPRK | WDR17 |
| NUP54  | PPP1R13B | RNF180 | SLTRK2 | TBC1D3B | TRAJ31 | WDR48 |
| OBL1   | PPP1R36 | RNF19A | SLTRK3 | TBC1D3B | TRAJ39 | WFDC6 |
| OG11   | PPP1R3A | RNFF2  | SLTRK4 | TBC1D3C | TRAJ43 | XIPI2 |
| OIT3   | PPP1R42 | RNF213 | SLTRK5 | TBC1D3F | TRAPPC12 | YAE1D1 |
| OLFM4  | PPP1R7 | RNF216 | SLTRK6 | TBC1D3H | TRIP12 | ZAN |
| OMG    | PPPR19A | RNF220 | SMARC2A | TBC1D3K | TRPM6 | ZBTB10 |
| OR4A5  | PPP3CB | ROBO2  | SMARC4 | TBC1D5 | TSC2D3 | ZC3HAV1|
| OR4C16 | PPP3CC | RP1    | SMG1   | TBR1   | TSEN2  | ZCCH11|
| OR5G5  | PRDM12 | RPRGR  | SNAP91 | TRB1   | TSH23  | ZFAND3|
| OSCP1  | PRDM2  | RUSC1  | SNCAIP | TCN1   | TSPAN17 | ZFP1   |
| OTTO   | PRELP  | RYR2   | SNE1D | TCM1   | TSPAN5  | ZFP2   |
| OVG1P1 | PREX1  | RY3    | SRNPA1 | TCT2   | TSPYL2  | ZFYV1 |
| 17x5N-hCR | S100PPB | SOCS4  | TEC   | TCTA   | TTC1   | ZFYVE28|
| PAN3   | PRL    | SALL4  | SON    | TECTA  | TTD1   | ZIC4   |
| PAPDS  | PSMD1  | SCARB1 | SOWADH | TETK1  | TTD8   | ZM1Z2  |
| PAPP-AS1 | PSMD3 | SCP2   | SP4   | TENM3  | TFDL4  | ZMYM6  |
| PARG   | PSFM1  | SCRN3  | SPATA16 | TENM4  | TTL5   | ZN13  |
| PAR2   | PTPRB  | SDA1D | SPDYA  | TESK1  | TXMNG  | ZNF23 |
| PAR3   | PTPRD  | SEC1A6 | SPEC1 | TES15  | TNIP   | ZNF347  |
| PAWR   | PTPQR  | SEC24B | SPRY1 | TEX2   | TXN4A  | ZNF518A|
| PCDH7  | PUM1   | SEZ2L1 | SPSB1 | THEG   | UBAC1  | ZP1F1 |
| PCDHAC2 | PXDN  | SGOL2  | SPTBN4 | THRAP3 | UBE2Q2 | ZNFG1 |
| PCDHGA3 | PXDLN | SHBP5  | SRBPB | THSD7B | UBE4A  | ZNFG1A |
| PCSK2  | PXMP4  | SHD15  | SSH1  | TING1L | UBENX  | ZNFG2 |
| PED3A  | PYGO1  | SHGLB1 | STAR2 | TKT    | ULK4   | ZNF3 |
| PEAI1  | P2P    | SHANK1 | STA2  | TLR10  | URB2   | ZPD1 |
| PEG10  | QSER1  | SHCBP1 | STS2A | TLR2   | USO1   | ZEDA |
| PKFB2  | RSHDM2 | SHOC2  | STS2A | TLR3   | USP11  | ZXD8 |
| PGBD2  | RAB3GAP1 | S1   | STSM1 | TM4SF8 | USP12  | ZZFE1 |
| PHACTR1 | RANBP17 | SIN3A | STSM2 | TMC01  | USP13  | ZZZ3  |
| PHF2   | RAPGEF2 | SIN3B | STSM3 | TMC02  | USP26 |
| PIK3CB | RBM12  | SIA1L1 | STSM4 | TME106B | USP24 |
| PIK3R1 | RBM27  | SICI   | SULF1 | TME178B | USP32 |
| PJA1   | RBM28  | SLC18A1 | SULF2 | TME2 | USP29 |
| PJA2   | RBM51  | SLC26A9 | SUMO4 | TME57 | UTRN |

The top 17 listed on Fig. 1 from 8N-hCR to 5N-hCR are in bold font; the 49 genes with 4N-hCR are underlined. A total of 699 genes on this list have 3N-hCR and are in normal font (not bold or underlined). 17x5N-hCR, 49x4N-hCR, 699x3N-hCR. Each N-hCR-bearing-gene and its corresponding protein in the NCBI homologene database, were used in this analysis except for the following 28 genes: APOL1 isX1, X2; ANKRDK28 icRA_g; C1orf56/FAAP20 v4X1,2,3; DMKN is5; FBXO38 icRA_d; FBKP7 isf23 AF100751.1; IGLV10-54 BAA19993.1; KHRD852 icRA_c; loc102725117 isf1-7; LRTOMT isf1c,1a; MARCH1 isf1,1a; MARCH5 isf1; MAMG int ix1; MIBKCH AAD345019; NTRK3 isof x10, XP_006720612; PAAAS-AS1 AAV415021; PTPRB IX5; PHACTR1 IX6; RAPGEF2 IX7; RNF128 isf2; SHD19 isx2,4,5,6,8; SNAP91 isfD; TRAJ31,39,43 AAB867655.1, AAB867581, AAB867541; VEZF1 icRA_a; WFDC6 icRA_b; WDR17 ix5; XIPI2 tv5 and tv3; ZFP1 ix1. A number of N-hCR-bearing-genes are in GTPase, GPCR or odorant receptor families, or can be grouped as involved with innate immunity and aneurysms (393) and another notable genes devoid of Asn codons in an immune system (387). Other notable genes devoid of Asn codons are mus APRT (kidney stones) (388) and human BIRC7 (ALL prognosis) (389), LOR (cf. Staph. aureous infection of nares) (390), SEP11 (cell cycle) (391), TCL1 (leukemia) (392), CSF3 (innate immunity and anemysus) (393) and KLF16 (proposed master metabolic regulator KLF14) (394).
diabetic retinopathy (94), and glucose metabolism (indirectly regulated by mTOR) (95). Finally, a gene with the third longest N-hCR in the mosquito genome (XM_316513) is translationally regulated (perhaps at its N-hCR) in insect midgut in response to plasmadium infected blood meals (96). The gene is homologous to human FAF1/TNFRSF6 which is associated with diabetes (97) and Parkinson’s disease (PD) (98).

Human genes with hCR have been linked to complex diseases (1). Genes that may respond to fluctuations in amino acids other than Asn (99-106), include CNDP1 (107,108) (L-hCR), MECP2 (109) (A.G.H-hCR), and HTT (Q-hCR) (110). The gene list could also extend to DMPK/ SIX5 (111,112), GCLC (89), FMRI (113) and C9orf72 (114-116) if unorthodox, repeat-associated-non-ATG (RAN), translation of upstream codon repeats (117-120), or alternate transcript variants (121) are included.

The HTT locus mediates the deleterious effects of Huntington’s ataxia, and is one of the early examples of a gene containing an hCR associated with a disease (122). It has a Q-hCR whose length can vary inversely with the age of onset and severity of the ataxia. The 23Q-hCR of HTT is situated in its ramp region, with a 16 codon interval between the hCR and the initiator AUG. Although much of the effort to understand Huntington’s disease has focused on aggregation of products of the HTT locus (123,124), the etiology of truncated translation products resulting from ribosomal stalling in the Q-hCR has received much less attention. Exon truncation fragments may arise if HTT is expressed in an environment of limiting Gln (22,125) and the resulting increase in neuronal cell death (126), could accelerate the onset and clinical course of Huntington’s disease (127,128).

2. ASNase produced by the biome. The potential for N-hCR-bearing genes to cause side-effects

ASNase production by Salmonella, pancreatitis, immunosuppression. Genetic studies suggest an environmental component for the etiology of diabetes (129) and the gut microbiome has been proposed to regulate human physiology, e.g. bone mass (130). An individual’s microbiome may also produce enzymes that alter host Asn levels. Persistent salmonellosis in mice causes pancreatitis (131,132) which is a side-effect of therapeutic ASNase treatment (133,134). In addition, Salmonella mediates its own virulence (135) via a cytosstatic ASNase (16) and inhibits mouse T cell responses in a manner reversible by administration of Asn (24,136); this Salmonella mediated immune inhibition may reflect the immunosuppression noted in ASNase-treated rabbits (137) and rodents (138,139).

Elongation: pancreatitis, cystic fibrosis, dislipidemia, clotting, complement and neurodefunction; Notch, WNT and hedgehog. Allelic variation in loci encoding-N-hCR-bearing-genes, such as KCNA3, CFTR, SLC26A9, SCARB1, IRS2, F5, FGB and SHANK1, have been associated with diabetes, pancreatitis, lipodystrophy, vascular disorders and neurological changes (140-144). KCNA3 (I-hCR) encodes a potassium channel that has allelic variants associated with altered risk for ALL (145) in a certain (germ line RUNX rearranged) subset of children and its mouse homolog regulates energy homeostasis and body weight (146). KCNA3 is thought to have its structure and function affected during its synthesis by residence time of certain of its elongating domains in the ribosomal vestibule (147-149) (cf. KCNH4, SCARB1, and KCNH8). Pancreatitis and diabetes are associated, respectively, with CFTR and SLC26A9, the products of which physically and functionally interact. CFTR is an ion channel, closely related, by membership in the superfamily of ATP-binding cassette proteins, to the multidrug resistance transporter (MDR1) (150-153). Some MDR1 alleles contain a polymorphic synonymous codon substitution at Gly412 (C1236T), very similar in location to Asn416 in the N-hCR of CFTR. Such polymorphisms in MDR1 have been proposed (154) to affect its rate of translation elongation resulting in alterations in the conformation of MDR1 with concomitant functional changes in the profile of anticancer drugs that MDR1 transports (60). The N-hCR of CFTR, located in the regulatory insert (RI) between the membrane spanning domain (MSD) and the nucleotide binding domain (NBD) could, by analogy to the key MDR1 Gly412 substitution, alter translation rate at its Asn 415 to 418 region, under conditions of low Asn, to result in generation of CFTR protein folding variants (155) with altered function that may affect bicarbonate exchange (in co-assemblies with SLC26A9) (156-158), Salmonella susceptibility (159), and timing of cystic fibrosis (CF) disease onset (160).

A similar location of N-hCR, between MSDs and NBDs, is found in two genes that encode important ATP-regulated magnesin channels: TRPM6 and TRPM7. Allelic variation of the former has been associated with elevated risk of diabetes, osteoporosis, asthma, and heart and vascular diseases (161), whereas allelic variation of the latter has been associated with sudden cardiac death, QT interval prolongation and atrial fibrillation in individuals with African ancestry (162), and ALS and PD in Guam (163). TRPM6 can form heterodimers with, and regulate function of, TRPM7; the latter is a channel regulated enzyme that can be cleaved to modify histones (164,165). TRPM7 affects vascularization (166), and has been implicated in ovarian, breast, pancreatic and prostate cancer as well as in the metastasis of nasopharyngeal carcinoma (167). The NBDs of these ion channels, as well as the STAS domain of SLC26A9 (151) (which is thought to assemble and interact with the Regulatory domain in the NBD of CFTR), all have poly Asn regions separating them from portions of their hydrophobic MSDs, suggesting that translocation rate at the N-hCR, perhaps due to variation in Asn levels, may serve to modulate the chronology of the synthesis and assembly of the hydrophobic intracellular domains of these molecules.

Dislipidemia could be caused by altered translation of SCARB1. A list of fifteen candidate genes in which synonymous codon substitutions may be of functional consequence, perhaps due to altered translation rate affecting protein synthesis, includes not only MDR1 (Gly412 and Ile145) but also CFTR (Ile507 and ΔF508) (160) and SCARB1 (Ala350) (168). Rs5888, a synonymous substitution in SCARB1 of codon Ala350, adjacent to Asn349, is associated with increased risk of coronary artery disease (CAD) and ischemic stroke (169-171). Translation rates of CFTR and SCARB1 may be regulated not only at the synonymous codon substitutions above, but also, in response to Asn concentration changes, at their N-hCR. SCARB1 is a high density lipoprotein (HDL) receptor that participates in lipid metabolism and flux of cholesteryl
esters (172) into e.g. HDL particles that contribute to cell signalling (173) and thus it could mediate the dislipidemia that accompanies the therapeutic administration of ASNase (174). \textit{SCARBI} affects susceptibility to myocardial infarction (175) and renal cell carcinoma (176,177) activity of lipoprotein associated phospholipase A2 (Lp-PLA2) (178), and causes an anti-inflammatory effect in macrophage (179); it indirectly affects atherosclerosis (180), mitigates stress (181), and affects fertility (182) and macular degeneration (183). By influencing gut absorption of vitamins, it can affect vascular integrity and diabetes susceptibility (184-188). A similar synonymous codon substitution at Cys816 of IRS2, (rs4773092), is associated with an auditory component of schizophrenia (43); this supports the notion, with the usual caveats regarding RNA stability, that IRS2 may also be translationally regulated, for example at its N-hCR.

ASNase treatment produces side-effects that include vascular dysfunction. Factor V and fibrinogen are two of several coagulation and complement factors encoded by N-hCR-bearing-genes. Polymorphic alleles of \( F_5^{\text{N-hCR}} \) (encoding coagulation Factor V) have been linked to coronary artery disease (189), hippocampal degeneration (190) and thrombotic events in ASNase treated children (144,191). ASNase specifically reduces the synthesis rate of fibrinogen (18), see below, a subunit of which is encoded by \( FGB \). Thus inhibition by ASNase of the synthesis of at least two N-hCR-bearing-genes, \( F5 \) and \( FGB \), could potentially account for the vascular side-effects of ASNase administration. \( FGB^{\text{N-hCR}}, \text{GP1BA}^{\text{N-hCR}} \), encoding the platelet membrane receptor (von Willebrand’s factor) associated with ischemic stroke (192), and \( CD9^{\text{N-hCR}}, \) a gene involved in platelet formation (193), are candidate N-hCR bearing genes that could be examined for their genetic association with adverse vascular events attending ASNase treatment (as has been reported for \( F5 \), above). Coagulation proteins have long been considered potential risk factors of ASNase therapy (194). The steady state half-life of autologous iodinated fibrinogen is not affected by ASNase treatment and hence the observed reduction in steady state plasma fibrinogen concentration that produces the hypofibrinogenemia (195) observed after ASNase treatment is likely due to inhibition of fibrinogen synthesis (18). There are concordant studies in rabbits (196) and humans (197) regarding the rate of catabolism and synthesis of fibrinogen in response to ASNase, as well as studies on the proteomics of \( FGB \) and \( C3 \) in diabetics (198,199). N-hCR-bearing-genes encoding complement proteins may also contribute to other disorders such as retinal degeneration through effects on \( C3^{\text{N-hCR}} \) (200) to multiple sclerosis through effects on \( C7^{\text{N-hCR}} \) (201) and to uptake of pathogens such as glycosylated viruses or bacteria by any of multiple members of the lectin and alternate complement pathway on Table I such as \text{CLEC6A} (202), \text{CLEC9A} (203) \text{CLEC13B/LY75, MASPI and C1QB}.

Mitigating the effects of low plasma Asn, by altering the composition of intestinal microbiota (204) or by using amino acid supplements (23), may slow disease onset or progression in those at risk of diabetes or its complications. Dietary Asn supplementation may particularly benefit CFTR-null homozygotes or compound heterozygotes, who frequently present with diabetes at later stages of their disease (205). One of the N-hCR-bearing-genes in Fig. 1, \text{PHACTR1}^{\text{N-hCR}} has been linked to coronary artery disease (CAD) in diabetics (206). Diabetes and CAD are frequent comorbidities, as are diabetes and Alzheimer’s disease (72) perhaps due to a shared etiology originating in low plasma Asn concentration. There are two N-hCR-bearing-genes from Fig. 1 that are linked to PD and mood disorders: \text{SNCAIP}^{\text{N-hCR}} and \text{ANK3}^{\text{N-hCR}}. PD and diabetes are comorbidities, and abnormal glucose regulation has been reported in >50% of PD patients (207) perhaps due to altered Asn homeostasis; correspondingly, bipolar disorder treatment outcomes differ for patients with diabetes as compared to normal controls (208). PD and ALS often occur with dementia (209,210); a shared etiology may be responsible, due to altered levels of Asn, perhaps even through complement genes such as \text{C1QB}^{\text{N-hCR}} (211), or the balance between \text{C1QL2}^{\text{N-hCR}}, \text{C1QL3}^{\text{N-hCR}} (212) and \text{BAI2}^{\text{N-hCR}} and their non N-hCR bearing paralogs: \text{C1QL1} and \text{BAI3} (213).

Multiple genes encoding N-hCR have been linked to neuropsychiatric disorders, PD, aspects of schizophrenia, Alzheimer’s disease, mood disorders [\text{CDH9} (214), \text{GTF2I} (215) and \text{ALDH6A1}], neurological dysfunction (\text{CDKL5} and \text{TMEM106B}) (216,217), breast-cancer (234), diabetes and \text{CD9} (218), -B, -C (219), TTLL4 and \text{CDKL5} (220), large artery stroke (221), ischemic stroke (222), and ALS (223). Multiple genes encoding N-hCR have been linked to neuropsychiatric disorders, PD, aspects of schizophrenia, Alzheimer’s disease, mood disorders [\text{CDH9} (214), \text{GTF2I} (215) and \text{ALDH6A1}], neurological dysfunction (\text{CDKL5} and \text{TMEM106B}) (216,217), breast-cancer (\text{BRCA2}, \text{CEACAMS/CEA} (218), \text{CYP19A1/Aromatase} (219), \text{IRS2}, \text{CLEC10A} (220), \text{LRP6} and \text{TBC1D5} (221), spinal degeneration (\text{COIL}, \text{FBXO38}, \text{ITGAV}, \text{ASIC2}, \text{KIAA1217} and \text{CHAD}), age of onset of amyotrophic lateral sclerosis (ALS) (\text{TLTCL4} and \text{LAMA3}) (222), dementia in ALS (\text{TMEM106B}) (223) retinal dystrophy (\text{TTL5}) (224), large artery stroke (\text{TLT5} and \text{PHACTR1}) (225) decreased bone density in tamoxifen treated women (\text{LRP4} and \text{NCOA1}) (226), ovarian cancer (\text{TBC1D3} and \text{TBC1D3F}) (227) T cell anergy (\text{GRAIL}/\text{RNF128}/\text{isf2}) (228,229), asthma, autoimmune diseases, innate immune (231-233) and the link between innate and adaptive immunity (\text{FFGR2-A, -B, -C}) (234) suggesting a common etiology of altered Asn homeostasis may need to be considered for some of these conditions.

\text{LRP5}, \text{LRP6} and \text{APC} are encoded by N-hCR-bearing-genes involved in the Wnt pathway. Rotterlin, which is reported to accelerate the turnover rate of \text{LRP6} (235) (a Wnt signalling co-receptor) (236), could be co-administered with ASNase because it may potentially synergize with ASNase to focus the effect of ASNase on LRp6 mediated Wnt signalling (237). We hypothesize that by preferentially lowering the steady state level of LRp6, the combination of drugs could regulate (238) bone mass, cancer, cardiovascular health, vision, Alzheimer’s and multiple other diseases of aging. Notch and hedgehog signalling are also affected by N-hCR bearing-genes such as \text{DZIP1}, \text{MAML2}, \text{BOC} and \text{CDON}, and may present attractive targets for drug discovery via small molecules that accelerate turnover of specific proteins encoded by N-hCR bearing-genes, synergistically magnifying the impact of ASNase by altering the replacement rate and perhaps by establishing lowered steady state levels of the targeted protein. There is already a precedent for synergism of prednisolone with ASNase, which occurs by an as yet unknown mechanism. The half-life of WNT signalling complexes and the contribution of DSV to turnover of WNT coreceptors \text{FZD} and \text{LRP6} has recently been characterized (239).

The psychiatric disorders associated with ASNase treatment of adults (240) have been ascribed to ammonia toxicity and cerebrovascular-accidents (22,241,242). N-hCR-bearing-genes that affect nitrogen metabolism include \text{CPS1}^{\text{N-hCR}}, regulating the first committed step of urea-cycle entry, and \text{SLC6A8}^{\text{N-hCR}}, a creatine transporter. Impaired translation of either gene could
tend to cause ammonia toxicity due to urea cycle dysregulation. Indirect support for a link between elongation rate and altered mental status (cf. KIF3C,\textsubscript{Asn,acr}) (243, 244) comes from computational studies noting that SHANK-2 and SHANK-3, but not SHANK-1, demonstrate traditional 'codon-use-bias', suggesting that a translational regulatory mechanism may underly SHANK mediated autism spectrum disorders (245). Since SHANK family genes are associated with schizophrenia and SHANK-1, -2, and -3 are associated with autism, SHANK1,\textsubscript{Asn,acr} could mediate mental status changes through altered translation rate that could be caused by fluctuations in plasma Asn concentrations.

Adverse neurological outcomes have also been associated with N-hCR-bearing-genes ANK3, IRS2, SNCAIP, XIRP2, PPP1R9A and CACNA1-C. Low plasma Asn, via the 17 N-hCR-bearing-genes listed in Fig. 1, can thus also plausibly be linked to onset of age associated disorders from ALS (246-248) to PD (249) through COIL, PPP1R9A (250), QSER1 (251) and SNCAIP; dental caries and periodontal disease as a diabetes comorbidity through TMEI178B or ANKRD17 in children (252,253); (cf. LRPIB and periodontitis in adults) (254). Also affected by LRPIB are age at menarche (255), APOE and fibrinogen binding (256), protection from cognitive decline in aging (257) as well as BMI, insulin resistance, optic disc size/area (cf. glaucoma), conditional erectile dysfunction in African American men, heart rate and multiple cancers. Deafness (258,259) is affected by XIRP2 (cf. Xeplin, PTPRQ), heroin addiction vulnerability in African Americans (260) and heart disease by XIRP2 (261,262); heart disease by PHACTR1 (263) (cf. LRPIP6) and PPP1R9A (cf. CHRM2, -3) (264); bone density by PHACTR1 (cf. LRPIP4, LRPIP5); erythropoesis and quality control of mitochondria by BNIP3L; nucleic acid processing by COIL, PAPD5, THRAP3, MEX3B and Clor686/FAAP20; and diabetes by TRAP3 (cf. CHRM3), PTPRD and IRS2.

BNIP3L and PEG10: cancer and frameshifting. The discussion above has focused on adverse events elicited by ASNase therapy, not the induction of tumor remission. Two N-hCR-bearing-genes, PEG10 and BNIP3L, have transcripts with long N-hCR that are encompassed within their initial two dozen codons. Both BNIP3L and PEG10 are apoptosis-related genes that are candidates for mediation of the cell death that has been observed to follow depletion of Asn either in cell culture (265) or in pediatric ALL. Multiple other N-hCR-bearing-genes are also potential targets, e.g., APC, (ARID5B, IL9R and RYR2) (266), JAK2, KCNA3 (145), UBE2Q2 (267), COIL (268) or SMG1,\textsubscript{Asn,acr} (269) (a Ser-Thr kinase with homology to mTOR). Temperature sensitive mutants of Asn tRNA synthetase undergo cell cycle arrest in early S phase at the nonpermissive temperature, a phenomenon that has been posited to be consistent with the existence a protein required for cell cycle progression that is highly sensitive to the level of charged Asn-tRNA (270), such as one encoded by an N-hCR-bearing-gene that is eliminated and must be re synthesized once per cell cycle (cf. COIL above).

3. Evidence for and against the model, caveats

In vitro translation and in vivo half lives are consistent with ASNase impaired translation at N-hCR. ASNase in E. coli, as well as in other gram negative bacteria (Salmonella, Klebsiella) (271), is encoded by two independent genes AsnA and AsnB. The AsnB product is periplasmic and is the therapeutic enzyme whereas the AsnA product is a cytoplasmic enzyme with a lower $K_m$ (272). Studies of a cytostatic factor produced by Salmonella led to its isolation and identification as ASNase, virtually identical to the AsnB product of E. coli. When added to in vitro translation extracts, it inhibited protein synthesis (16). To determine how it inhibited protein synthesis, i.e. if it simply depleted the levels of asparaginylated tRNAs available for translation, or if the process was more complicated (273,274) in vitro translation experiments (unpublished data) were performed with defined templates containing Asn codons at predetermined sites. T7 RNA polymerase was used to generate transcripts that were either devoid of Asn codons or contained one, two, five or 23 Asn codons between the N- and C-terminal segments of a bipartite hybrid protein composed of two human genes with no Asn codons. The N-terminal portion was derived from TCL1A, and the C-terminal portion was derived from CKS2. The central, intragenic N-hCR was, on occasion, substituted by the programmed ribosomal frameshifting (PRF) region from PEG10 which contains an Asn (AAC) codon at the frameshifting site. The resulting in vitro transcripts were translated in rabbit reticulocyte cell free lysates with isotopically labelled $^{35}$S-methionine and the products were analyzed by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis followed by autoradiography. This template gave extremely clean IVT results without the partial products seen with other templates such as PEG10 or gauvia luciferase. It was determined, with some appropriate control experiments, that there were quantities of ASNase that could be added to the translation mix to create different ratios of partial to full length products which could reflect relative degrees of pausing at the different poly Asn regions of length zero, one, two, five and 23 codons. Free Asn could subsequently be added back to the depleted reaction mix to ‘chase’, to a first approximation, the short ‘TCL1A’ proteins into longer, hybrid, ‘TCL1A/CKS2’ proteins. Conditions were also established in which the relative efficiency of frameshifting at the Asn codon of the PRF site of PEG10 was affected by exogenous ASNase added to the in vitro translation reaction, but this result was far less compelling than the effect of ASNase on translation at N-hCR.

We have seen full length translation of templates devoid of Asn codons under conditions of exogenously added ASNase, but in templates containing Asn codons, translated under identical conditions, we observe translation that extends to the N-hCR. Thus we suggest that depletion of Asn-ylated tRNA is likely to be the underlying cause of inhibition of synthesis seen previously by use of random, mixed templates for characterizing the inhibition, by Salmonella ASNase, of in vitro translation reactions (16). There were also unanticipated findings suggesting that frameshifting efficiency may depend on the number of Asn codons in an artificial N-hCR that was inserted a dozen codons upstream of the PEG10 frameshifting site. We have not characterised the behavior of deamidated Asn-tRNA\textsubscript{Asn} which could incorporate Asp residues at Asn codons were it not edited and removed by a proofreading complex.

Differences in response to ASNase administration in children and adults, a recent gene family expansion. There are differences in response to ASNase between children and adults. They
are most obvious in the ALL tumor remission response, as well as in the type of glycemic dysregulation: peripheral vs. central loss of responsiveness. In the pediatric patients, the hyperglycemia is insulin reversible, insulin is absent from circulation following an ASNase therapeutic regimen that includes steroid hormones similar to prednisolone, and it is likely that central control over insulin synthesis or release may be deficient. In the metabolic studies of diabetic adults, Fasting Insulin levels are high, and IRS2 mediated peripheral signalling may be deficient. In addition, the unacceptable neurovascular complications (fugue state, cerebrovascular accidents) in adults compared to children underscores the difference between the physiology of children and adults.

The evolutionarily recent duplication of the TBC1D3\textsubscript{N-hCR} gene of hominids, and the expansion, and perhaps positive selection in humans, of eight members of this N-hCR bearing-gene family (275), suggests that these oncogenes (associated with ovarian cancer) (227) whose turnover is regulated by palmitoylation (276), may control vesicle fusion by noncanonical regulation of RAB GTP exchange (277), perhaps in association with Rab5 (278) [cf. TBC1D5 with Rab7 (279) or autophagy with ATG-8 (280) or ATG-9 (280)]. TBC1D3 is involved in pinocytosis with ARF6 (281), affects epidermal growth factor receptor (EGFR) signalling by altering microtubule dynamics (282) and can influence insulin signalling (280) by regulating IRS1 degradation (284 cf. 285). These genes could also potentially regulate insulin or amino acid release from vesicular or lysosomal storage (286).

\textit{AAC codons; intrinsically disordered protein assemblies.} Most of the poly Asn codon runs reported here consist of the two isoacceptor codons AAT and AAC used in about equal frequency with a slight bias towards homopolymeric runs of AAC. In the gene IRS2\textsubscript{N-hCR}, from human, zebrafish, elephant-shark, frog, python and falcon, AAC is used exclusively in N-hCR runs of varying length and distance from the initiator methionine, suggesting that if regulation is not restricted only to the AAC isoacceptor species, perhaps there is a further, structural, component to this phenomenon [CAG homocopolymer encoding poly Q repeats can form triple stranded structures (287), RNA sequences enriched in AAT motifs can be labile (288)]. Interestingly, \textit{PEG10\textsubscript{N-hCR}} and BNIP3L\textsubscript{N-hCR} employ AAC codons exclusively in human and mouse \textit{(PEG10)}, or in human, mouse, rat, lizard, -frogs and chicken (BNIP3L), indicating that the two isoacceptor tRNAs may indeed be differentially regulated.

N-hCR-bearing-genes encode proteins that engage in networks whose equilibria may be affected by elongation rate, e.g. PPI1R9A\textsubscript{N-hCR}, unique among the 17 genes of Fig. 1 because of two separate N-hCR, encodes neurabin, the intrinsically disordered regions (289) of which become conformationally restricted in regulatory complexes with PPI (290), and which is implicated in neurite formation (291), neuroprotection against seizures (292), mood disorders (293), hippocampal plasticity (294), long term depression (295), dopamine mediated plasticity (296), contextual fear memory (297), hepatoesplenic lymphoma (298) and regulation of G protein coupled receptor (GPCR) signalling (290). A key unstructured UBZ domain of Fanconi's anemia gene FAAP20 can form a highly structured α helix upon ubiquitin binding; this domain is interrupted by a 5N-hCR in certain variant isoforms. The 2N-hCR of TP53 is similarly located: adjacent to a pair of transactivation domains (TADs) that gain structure upon ligand binding (299,300). The N-hCR of TRPM-6 and -7 interrupt their α kinase domain. Modulating translation rate by varying Asn concentration, while synthesising these proteins, could allow modulation of the protein assemblies in which these proteins participate.

\textit{Caveats, Asn residues can be post-translationally modified; interspecies N-hCR length variation and inflammation.} In this survey of other potential roles for the conserved poly Asn regions in proteins, we note that they also act as sites of post-translational modification to regulate protein activity by glycosylation or deamination or (cleavage, by Asparaginyl endopeptidases (301) (cf. Taspase, an ASNase gene family member) (302)). The 4N-hCR of CFTR, differing in length between human, mouse and pig, encodes a conformationally dynamic regulatory insertion (303) that may gate access to the ATP binding site (304). A similarly unstructured loop in Bcl-xL undergoes deamination (305,306), as does an Asn residue pair between the TADs of TP53 (307), a region unstructured until bound to MDM2 (308,309). The 2N-hCR of TP53 differs in length between rats, mice and humans. N-hCR length variation in N-hCR-bearing-genes can correlate with disease severity in animal models of human inflammation. For example the pig model of CF more closely reflects the physiology of the human disorder, in comparison to the mouse model (310) perhaps because, as with TP53, the length of the poly Asn region in pig more closely resembles that of human rather than mouse. Also, in \textit{P. aeruginosa-induced} bacteremic shock, TXNIP exacerbates septic shock associated with bacteremia in a mouse model (92). TXNIP of mouse has an identically situated, but longer poly Asn region (8N-hCR) than human and most other nonrodent mammals (3N-hCR), perhaps enabling greater redox level changes in response to Asn level variation. These examples may reflect divergent evolutionary choices in inflammatory and pathogen response strategies that may partially explain the reported differences between human and rodent models of inflammation (311,312) and IRS2 genetic associations (72). Altered electrophoretic mobility, a hallmark of some deamination events, indicates that post-translational modification may even occur at the poly Asn region of IRS (281). Deletion analysis of the N-terminal poly Asn containing region of \textit{BNP3L/B5/NIX} suggests that it masks apoptosis inducing function (313,314). Regarding self association and aggregation at poly Asn regions, Perutz stated that it is unlikely that poly Asn repeats can form polar zippers of the kind formed by poly Gln repeats (315), but see (316). hCR may be tolerated at intrinsically disordered regions of proteins (317) where proteins could accommodate hCR expansion in their genes (318). An alternative explanation for the action of ASNase: NH3 generated by ASNase may act as a gaseous reactive signalling molecule, akin to NO, CO or H2S, to modify protein structure and function (319).

4. Biochemistry of amino acid activation, genome-wide association studies
At least five different human tRNA synthetases can serve as autoantigens in inflammatory responses (320). Human tRNA
synthetases AsnRS and HisRS both serve as chemoattrac-
tants (321), ligands for cell surface proteins CCR5 and CCR3
respectively (322). AsnRS protein levels are upregulated by
almost three orders of magnitude in a model of preosteoblast
cell proliferation driven by FGF2 (323). Filarial AsnRS, in
contrast to human AsnRS, serves as a ligand for CXCR1 and
CXCR2 and is chemotactic for neutrophils and eosinophils,
with a terminal subdomain that serves as a ligand for human
IL8 receptor (324). The link between inflammatory responses
and Asn tRNA synthetases remains an open question.

Leu contributes to formation of mTORC1, a biochemical
complex that regulates cell cycle (325) in conjunction with
other amino acids (326,327) including Arg (328,329) and
Gln (105,330-332). In a related experimental paradigm,
apoptosis induced by Gln withdrawal, Asn, instead of Gln
may actually be the effector molecule whose withdrawal is
sensed (267). A biochemical mechanism for sensing Asn levels,
required either to trigger apoptosis, or to advance through
S phase of the cell cycle, perhaps mediated by AsnRS, and not
involving ribosomes may yet be discovered, but even if such
a mechanism were to exist, translational inhibition at N-hCR
would still remain a most parsimonious explanation for the
myriad clinical side-effects of ASNase treatment. Poly Asn (2)
and poly Leu (100) codon repeats (N-hCR and L-hCR) appear
in a biased manner in mammalian genomes; this bias may be
related to metabolicomic differences in the levels of Asn (23,28)
and Leu (333) between normal and diabetic patients as we have
discussed for the case of Asn in this study, and as may be the
case for Leu (cf. L-hCR length polymorphisms and diabetic
nephropathy in CNDP1 (107,108), mTORC1 activation is the
orthodox pathway for understanding how altered amino acid
levels exert metabolic control. This study has examined an
alternative hypothesis, of the potential for amino acid fluc-
tuations to control translation rate, to thereby effect a different
measure of metabolic control by reshaping the composition of
the proteome.

**Genome-wide association studies (GWAS).** GWAS have
met limited successes (190,334-336). The contribution of
the environment to gene expression is particularly difficult
to quantify but it may explain the missing heritability
problem (337). The biomic environment has a significant
impact on gene expression, and part of its function could
be to alter levels of plasma amino acids that may ultimately
be reflected in intracellular amino acid level variation and
alterations in translation rates within those cells. If the genomic
bias in N-hCR use is a harbinger of a broad effect of inhibited
translation due to Asn level variation, then GWAS screens
for common disorders may reveal N-hCR-bearing-genes that
could be influenced by constituents of the biome that alter Asn
concentrations and could contribute to metabolism, aging and
complex diseases.

GWAS of five major psychiatric illnesses implicates
four N-hCR-bearing-genes (338). Most prominent is ANK3
(one of the top 17 N-hCR-bearing-genes (cf. Fig. 1) as
well as CACNA1C, ZFPM2 and NTRK3. NTRK3 can be
related, through a neuronal cell death mechanism (339), to
mBEX3 (340), a murine gene that bears a long N-hCR. NTRK3
is associated with Gaucher's disease, PD (341,342), multiple
cancers (343-347) leukemia (348), and is an entry receptor for
trypanosomes (349) (cf. ANK3, PTPRD, PHACTR1) (350).
Asn level variation may affect all of these processes. In a
GWAS of seven common diseases, hypertension was most
closely associated with two linked N-hCR-bearing-genes, RYR2
and CHRM3. RYR2 is involved with heart disease (351) and
associated with lipid levels (352) and ALL (266), CHRM3
is associated with response to an antidiabetic drug in African
Americans (353) (cf. CHRM2, CHRM3 associated with metabolic
syndrome) (354). Another of the seven common diseases,
Crohn's disease, was quite significantly associated with an
N-hCR-bearing-gene, IL23R (355). IL23R is also associated
with psoriasis, diabetes (356), CAD, Behcet's disease, anky-
losing spondylitis (357-359) and leprosy (360).

A GWAS of ALL shows that it is affected by at least
two other N-hCR-bearing-genes, in addition to RYR2 (noted
above): IL9R (361) and ARID5B (cf. KCNA3) (145). IL9R shares
a common γ subunit with other interleukin receptors (362)
IL9R has a 4N-hCR that is absent from all mammals except
Pan (cf. APOL1 which lacks 3N-hCR in all mammals except
Gorilla (2N in Pongo), ARID5B encodes part of a histone
lysine demethylase complex (363) and is not only genetically
associated with ALL (266,364-369) but is also associated with
conveal changes (370), low birth weight (371), diastolic blood
pressure (372) rheumatoid arthritis (373), response to halo-
peridol (374) (an anti-psychotic medication), systemic lupus
erythematosus (SLE) (375), lipid balance (376) and triglyceride
metabolism in mouse adipocytes (377), as well as, in humans,
T2DM (378). The contribution of ASNase to these conditions,
especially to ALL, potentially by altered translation at the
N-hCR of ARID5B warrants further investigation (379).

We propose that the impaired translation which has been
described above be termed the ‘translational N-hamper effect'
because there is nothing intrinsically impaired about a protein
polymerization reaction in which one of the required com-
ponents, activated Asn tRNA, is ratelimiting for the translocation
reaction on the template mRNA. The verb of choice for slowed
translocation could just as well have been cumbered move-
ment instead of hampered movement. If the argument was first
made for Gln, the Q-cumber effect could have encompassed
this hypothetical phenomenon.

The ‘translational N-hamper effect’ is a mechanism
whereby protein expression is modulated by coupling fluc-
tuations in appropriate aminoacylated-tRNA availability to
ribosome translocation rates at corresponding hCR. Thus,
ribosome movement could pause at hCR which would serve
as punctuation marks to allow relative intracellular amino acid
pool sizes to influence mRNA decoding and protein synthesis.
Amino acid level fluctuation could potentially affect: mRNA
halflife and accessibility to regulatory complexes, ribosome
frameshifting efficiency, initiation rate and formation of stable
translation complexes, and elongation rate and vesicle resi-
dence time to affect steady state levels of these proteins and of
higher order structures in which they participate.

Our model holds that Asn level reductions, such as those
accompanying the administration of ASNase, cause impaired
translation of N-hCR-bearing-genes to precipitate metabolic,
vascular, immunological and neurological disorders and
contends that this could result in insulin desensitization, impaired
insulin release and, ultimately, diabetes. Thus the microbiome,
by endogenously generating ASNase, could cotranslationally
regulate a constellation of N-hCR-bearing genes to initiate complex disease pathologies.

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