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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.

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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

N-hCR size GENE	Diabetes Metabolsm Growth	Mitochon Membrn	Neuro & Psychiatric Associations	Cancer Immunity	CoronArteryDis Blood Bone	Partn Dom	DNA Damage	RNA Metabolism
8N h-CR:								
IRS2	Diabetes		Aud. halucinations Schizophrenia Hipocampl Plasticity	Multiple Ca	CAD, *IRS1*-Erythropoesis	PDZ		
7N h-CR:								
PEG10		SIAH1 apopt		Hepato Ca. Burkitt's	Angiogenesis Placentation			
6N h-CR:								
VEZF1				IL3 promotr	Angiogenesis		Methylation	Pausing polII
5N h-CR:								
BNIP3L		Mito apop		Glioma	Erythropoesis			Hypoxia Dicer
SNCAIP	Metabolism		Parkinson's disease Neurodegeneration			ANK		
PPP1R9A			Hippocampl plasticity Contextual Fear Memory HTT Ataxia			PDZ		
ANK3			Mood disorders Schizophrenia			ANK		
ALS2CR11			adjcnt to *TMEM237*: Joubert's syndr Ciliopathy					
PHACTR1	Diab assoc. Cardiac dis.		Migraine	Breast Ca.	CAD Bone density			
PAPPA-AS1			adjcnt to ASTN2: Alzheimers schizophrenia		Placenta			
COIL	Short adult stature		Spinal Muscular Atrophy Spinal Motor Neuron ALS				Cisplatin cell cycle	Telomrase snRNP Gems
XIRP2		Claudin	Heroin addiction risk Deafness		Cardiac remodeling	LIM		
TMEM178B		Claudin		Dental caries				
PAPD5				mir21 polyA			Camptothecn	Rna Process'g
THRAP3	Diabetes PPARγ						DNA Damge Response	Mediator Rna Process'g
MEX3B	Muscle excess	NCadhrn Conxin43		Endomtr Ca.	Blood testes barrier			Long non coding RNA
c1orf86 *FAAP20*				Leukemia	Fanconi Anemia	UBZ	Crosslink Repair	

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, fiabetes 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 N-hCR bearing 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, BAI2, BMPR2, C2orf61, CD9, CFTR, CHRM2, CNOT10, EOMES, EPPIN, EPPIN-WFDC6, EVI2A, FAM193A, FRS3, GTF2I, IL9R, KIAA1841, KIF3C, KLF17, LEMD3, LRP6, MAML2, MYRF, NCOA1, PARP3, PEAK1, PPP1R13B, RNF103, SH3D19, SI, SLIT1, SLIT2, SLIT3, SNAP91, TAB2, TAB3, TAX1BP1, TEC, TMEM57, TOX3, TRPM6, TRPM7, TTC8, TTLL5, UBE4A, ZXDA, ZXDB* Unorthodox human proteins deserving closer attention are from unusual cDNAs: $Map3K2_{4N\text{-}hCR}$ AAH65755.1; $TCR\alpha_{5N\text{-}hCR}$ AIE11180.1; $V\kappa_{5N\text{-}hCR}$ AAO11865; and $V\lambda_{4N\text{-}hCR}$ AAD29331.1. The germline V regions of immunoglobulin (Ig) λ 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); *CACNA1D* (M-hCR); *HSD11B1* (Y-hCR); *NR4A3* (H-hCR); *TAF9, URI1, ASPN, EFTUD2, GLTSCR1L, THBS4* (D-hCR); *HRC* (D-, E-, H-hCR); *ATAD2* (S-, D-hCR); *EIF5B* (K-, D-, E-hCR); *KCNMA1, MAP3K1, CXXC4, WDR26, TNRC18, SRRM2* (S-, T-, G-hCR); *CACNA1A* (H, N, Q-hCR); *POU4F2* (M-, G-, H-, S-hCR); *POU3F2* (G-, H-, Q-hCR); *SKIDA1* (H-, E-, A-hCR); *USP34* (H-, N-hCR); *ATXN1, ATXN2, ATXN3, ATXN7, AR, KMT2D, KMT2C, MAMC2, MAML3, FOXP2, ARID1A, ARID1B, ARID3B MED12, MED15, NCOA3, NCOA6, IRF2BPL, VEZF1, ABCF1* and *HTT* (Q-hCR). The hCR appear in proteins from the NCBI homologene (381) database.

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

significant hyperglycemia (500-700 mg/dl) when both drugs are administered in combination at doses that are insufficient to produce an effect above baseline (~100 mg/dl) when either drug is administered alone (27).

Complementing these clinical and experimental observations, metabolomic data from the Framingham Heart study and from diabetic patients in a Shanghai study have shown that plasma Asn concentration is negatively correlated with fasting insulin concentration (28), and that the degree of negative correlation is the highest for Asn by comparison with the 20 amino acids that are commonly incorporated into 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 correlatively 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, thrombopoetin, 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* deletion 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/muted 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 the initiator 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, *Cf.* 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 halflife, result indirectly in decreased steady state levels of such proteins. High rates of translation may even increase the halflife 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 neurodegeneration (20% with metabolic disorders, above), and eight percent with vasculature and hematopoesis. Of the remaing ~14%, many can be classified as involved with chromatin modification, DNA maintainance 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 $JAK2_{3N\text{-}hCR}$, hematopoesis (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),

Table I. Alphabetical listing of 765 human genes 3N-hCR and higher (>3N-hCR).

A2M	*ATP6V1C1*	*CES2*	*DNAH1*	*FSIP2*	*KHDRBS2*	*LY75*
AATK	*BAG5*	*CFAP45*	*DNAH6*	*FSTL3*	*KIAA0232*	*LYST*
ACACA	*BAG6*	*CFAP54*	*DNAJB11*	*G3BP1*	*KIAA1024L*	*MALT1*
ACACB	*BAI2*	*CFTR*	*DNAL4*	*GABBR1*	*KIAA1107*	*MAML2*
ACAN	*BCAS1*	*CGRRF1*	*DNM1L*	*GBP6*	*KIAA1210*	*MAP7*
ACSBG2	*BCAS3*	*CHAD*	*DNMT3A*	*GCLC*	*KIAA1217*	*MAPK8IP2*
ADAM10	*BIN2*	*CHD7*	*DNTTIP2*	*GDPD1*	*KIAA1549L*	*MAPRE2*
ADAM19	*BIRC6*	*CHEK2*	*DOCK4*	*GGA1*	*KIAA1586*	*MARCH1*
ADAM30	*BMPR2*	*CHFR*	*DRD1*	*GGA3*	*KIAA1671*	*MARCH6*
ADCY8	***BNIP3L***	*CHRM2*	*DSCAM*	*GIN1*	*KIAA1841*	*MASP1*
ADCY9	*BOC*	*CHRM3*	*DSPP*	*GIT2*	*KIDINS220*	*MBD5*
AEBP1	*BOD1L1*	*CHRNB1*	*DUSP10*	*GJA9*	*KIF16B*	*MDGA2*
AFF2	*BRIP1*	*CHRND*	*DUSP21*	*GK*	*KIF1A*	*MED1*
AGAP1	*BRCA2*	*CHSY1*	*DYNC1H1*	*GKN1*	*KIF21A*	***MEX3B***
AGBL2	*BTAF1*	*CKAP2L*	*DYNC1I1*	*GNAZ*	*KIF3C*	*MGAM*
AKAP4	*BTBD1*	*CLCA1*	*DYNC1I2*	*GNPAT*	*KLF17*	*MGAM2*
ALDH6A1	*BTBD2*	*CLCA2*	*DYRK4*	*GOLPH3*	*KLHL3*	*MGAT2*
ALKBH8	*BTBD3*	*CLCA3P*	*DZIP1*	*GP1BA*	*KLHL30*	*MIB1*
ALPK2	*BTG4*	*CLCA4*	*ECM2*	*GPATCH2*	*KMT2A*	*MID1*
ALS2CR11	*C18orf63*	*CLEC10A*	*EFNB2*	*GPR112*	*KMT2E*	*MIS18BP1*
AMBRA1	***C1orf86***	*CLEC6A*	*EIF2A*	*GPR126*	*KNG1*	*MITF*
AMY2A	*C1QB*	*CLMN*	*ELAVL2*	*GPR64*	*l101060321*	*MLLT3*
AMY2B	*C1QL2*	*CLTC*	*ELF1*	*GPR82*	*l101060389*	*MON2*
ANAPC7	*C1QL3*	*CNOT10*	*EOMES*	*GSG2*	*l102723859*	*MTBP*
ANK3	*C2orf49*	*CNOT2*	*EPCAM*	*GTF2I*	*l102724862*	*MTCH1*
ANKFN1	*C2orf61*	*CNOT6*	*EPPIN*	*HACL1*	*l102725117*	*MTERF1*
ANKFY1	*C3*	*CNOT6L*	*EPPIN-WFDC6*	*HAVCR1*	*LAMA3*	*MTG2*
ANKRD17	*C3orf67*	*CNST*	*EPRS*	*HCFC2*	*LAMB4*	*MTNR1A*
ANKRD28	*C5orf67*	*COBL*	*EPYC*	*HECTD4*	*LAMC2*	*MTTP*
ANKRD44	*C7*	*COBLL1*	*EVI2A*	*HERC6*	*LAMP2*	*MTUS2*
ANKRD7	*CACHD1*	***COIL***	*EYA1*	*HERPUD1*	*LARP4*	*MUC19*
ANPEP	*CACNA1A*	*COL24A1*	*F5*	*HERPUD2*	*LEMD3*	*MUC3A*
ANTXR1	*CACNA1C*	*COL6A2*	*FAM117B*	*HLA-DPA1*	*LGI1*	*MUC4*
ANTXRL	*CACNA1D*	*COL6A5*	*FAM126A*	*HLTF*	*LGI3*	*MXRA5*
AP2B1	*CACNA1F*	*COX19*	*FAM171B*	*HMCN1*	*LGR6*	*MYO10*
AP4E1	*CACNA1H*	*CPEB4*	FAM193A	*HNRNPL*	*LIMS2*	*MYO19*
APBA2	*CACNA1S*	*CPM*	*FAM208B*	*HNRNPUL1*	*LINGO2*	*MYO1A*
APC	*CALHM1*	*CPNE9*	*FAM65B*	*HRG*	*LITAF*	*MYO1B*
APCDD1	*CARF*	*CPS1*	*FAM69C*	*HSD3B1*	*LPHN2*	*MYO1E*
APOB	*CASC5*	*CPXM2*	*FANCI*	*HSPG2*	*LRFN2*	*MYO1F*
APOL1	*CASS4*	*CRTAC1*	*FAT2*	*HYPM*	*LRFN5*	*MYO6*
AQP5	*CASZ1*	*CSMD2*	*FAT3*	*ICE1*	*LRIG1*	*MYO9A*
ARHGAP11A	*CATSPERD*	*CSTF3*	*FAT4*	*IGDCC3*	*LRIG2*	*MYO9B*
ARHGAP20	*CCDC144A*	*CUL1*	*FBXL5*	*IGLV10-54*	*LRIG3*	*MYOM1*
ARHGAP24	*CCDC144NL*	*CUL3*	*FBXO27*	*IL1RAP*	*LRP1B*	*MYRF*
ARHGEF10	*CCDC18*	*CXCL12*	*FBXO38*	*IL23R*	*LRP2*	*MYT1L*
ARHGEF5	*CCDC36*	*CYP19A1*	*FBXO39*	*IL9R*	*LRP4*	*N4BP2*
ARHGEF6	*CCDC39*	*CYP1A1*	*FBXO48*	*ING3*	*LRP5*	*NBN*
ARID1A	*CCDC73*	*CYSLTR2*	*FBXO5*	*INTS12*	*LRP6*	*NBR1*
ARID1B	*CCDC88A*	*DCAF6*	*FBXW7*	*IPMK*	*LRPPRC*	*NCAM2*
ARID5B	*CCKAR*	*DCAF7*	*FCGR2A*	*IRAK3*	*LRRC30*	*NCAPH2*
ARMC3	*CCNT1*	*DCBLD1*	*FCGR2B*	*IRS2*	*LRRC37A*	*NCKAP1*
ARMC4	*CD63*	*DCN*	*FCGR2C*	*ISLR2*	*LRRC37A2*	*NCOA1*
ARPP21	*CD9*	*DDIAS*	*FCN1*	*ITGAV*	*LRRC37A3*	*NCOA3*
ASB2	*CDC14A*	*DDR2*	*FCRL4*	*ITGB1BP1*	*LRRC38*	*ND4*
ASCL5	*CDH9*	*DDX4*	*FEZ1*	*ITK*	*LRRC57*	*NECAB3*
ASIC2	*CDHR1*	*DDX42*	*FGB*	*JAK2*	*LRRC69*	*NEDD1*
ASPN	*CDKL5*	*DDX59*	*FKBP7*	*JMJD1C*	*LRRC70*	*NEURL4*
ATAD5	*CDON*	*DHX38*	*FLII*	*JMY*	*LRRC71*	*NFATC1*
ATF7IP	*CEACAM5*	*DIAPH1*	*FLRT1*	*KCNA3*	*LRRC72*	*NGLY1*
ATF7IP2	*CELSR3*	*DIDO1*	*FLRT3*	*KCNH4*	*LRRC8B*	*NIPA2*
ATL2	*CEMIP*	*DLGAP5*	*FNDC4*	*KCNH8*	*LRRN1*	*NKX2-5*
ATP2B1	*CENPC*	*DMD*	*FNDC5*	*KDM3A*	*LRRN2*	*NNT*
ATP2B3	*CEP350*	*DMXL2*	*FRS3*	*KDM6A*	*LRTOMT*	*NOD1*
ATP2B4	*CERS2*	*DMKN*	*FSHR*	*KDM6B*	*LTF*	*NOS2*

Table I. Continued.

NOTCH1	*PKDREJ*	*RDH10*	*SLC2A12*	*SUSD1*	*TMEM259*	*UTY*
NPNT	*PKD1L3*	*REG4*	*SLC35A4*	*SUZ12*	*TMOD1*	*VEPH1*
NPY1R	*PKHD1L1*	*RELA*	*SLC6A11*	*SYCP1*	*TMPRSS11A*	***VEZF1***
NPY6R	*PKP1*	*RGL1*	*SLC6A4*	*SYNPO2*	*TMPRSS11D*	*VGLL4*
NR1D1	*PLEKHG3*	*RLF*	*SLC6A8*	*TAB2*	*TMPRSS15*	*VN1R2*
NRK	*PLS1*	*RMI1*	*SLCO3A1*	*TAB3*	*TNRC6A*	*VPS13A*
NRP1	*PMS1*	*RNF103*	*SLIT1*	*TALPID3*	*TNRC6B*	*VPS4A*
NSUN7	*PNLIPRP1*	*RNF128*	*SLIT2*	*TANGO2*	*TOX3*	*VPS45*
NT5E	*POGZ*	*RNF139*	*SLIT3*	*TAS2R38*	*TPGS1*	*WDR13*
NTRK3	*PPAP2B*	*RNF157*	*SLITRK1*	*TAX1BP1*	*TPRKB*	*WDR17*
NUP54	*PPP1R13B*	*RNF180*	*SLITRK2*	*TBC1D3*	*TRAJ31*	*WDR48*
OBSL1	*PPP1R36*	*RNF19A*	*SLITRK3*	*TBC1D3B*	*TRAJ39*	*WFDC6*
OGG1	*PPP1R3A*	*RNF2*	*SLITRK4*	*TBC1D3C*	*TRAJ43*	***XIRP2***
OIT3	*PPP1R42*	*RNF213*	*SLITRK5*	*TBC1D3F*	*TRAPPC12*	*YAE1D1*
OLFM4	*PPP1R7*	*RNF216*	*SLITRK6*	*TBC1D3H*	*TRIP12*	*ZAN*
OMG	***PPP1R9A***	*RNF220*	*SMARCA2*	*TBC1D3K*	*TRPM6*	*ZBTB10*
OR4A5	*PPP3CB*	*ROBO2*	*SMARCA4*	*TBC1D3L*	*TRPM7*	*ZBTB6*
OR4C16	*PPP3CC*	*RP1*	*SMG1*	*TBC1D5*	*TSC22D3*	*ZC3HAV1*
OR8G5	*PRDM12*	*RPGR*	*SNAP91*	*TBR1*	*TSEN2*	*ZCCHC11*
OSCP1	*PRDM2*	*RUSC1*	***SNCAIP***	*TCHHL1*	*TSHZ3*	*ZFAND3*
OTOG	*PRELP*	*RYR2*	*SNED1*	*TCN1*	*TSPAN17*	*ZFP1*
OVGP1	*PREX1*	*RYR3*	*SNRPA1*	*TCTN2*	*TSPAN5*	*ZFPM2*
P2RY10	*PRF1*	*S100PBP*	*SOCS4*	*TEC*	*TSPYL2*	*ZFYVE1*
PAN3	*PRL*	*SALL4*	*SON*	*TECTA*	*TTC1*	*ZFYVE28*
PAPD5	*PSMD1*	*SCARB1*	*SOWAHD*	*TEKT1*	*TTC8*	*ZIC4*
PAPPA-AS1	*PSMD3*	*SCP2*	*SP4*	*TENM3*	*TTLL4*	*ZMIZ2*
PARG	*PSMF1*	*SCRN3*	*SPATA16*	*TENM4*	*TTLL5*	*ZMYM6*
PARP2	*PTPRB*	*SDAD1*	*SPDYA*	*TESK1*	*TXLNG*	*ZNF132*
PARP3	*PTPRD*	*SEC16A*	*SPECC1*	*TEX15*	*TXNIP*	*ZNF23*
PAWR	*PTPRQ*	*SEC24B*	*SPRY1*	*TEX2*	*TXNL4A*	*ZNF236*
PCDH7	*PUM1*	*SEZ6L2*	*SPSB1*	*THEG*	*UBAC1*	*ZNF347*
PCDHAC2	*PXDN*	*SGOL2*	*SPTBN4*	***THRAP3***	*UBE2Q2*	*ZNF451*
PCDHGA3	*PXDNL*	*SH3BP5*	*SRPRB*	*THSD7B*	*UBE4A*	*ZNF518A*
PCSK2	*PXMP4*	*SH3D19*	*SSH1*	*TINAGL1*	*UBXN7*	*ZNF804A*
PDE3A	*PYGO1*	*SH3GLB1*	*STAB2*	*TKT*	*ULK4*	*ZNRF3*
PEAK1	*PZP*	*SHANK1*	*STAU2*	*TLR10*	*URB2*	*ZPLD1*
PEG10	*QSER1*	*SHCBP1L*	*STK32A*	*TLR2*	*USO1*	*ZXDA*
PFKFB2	*R3HDM2*	*SHOC2*	*STK32B*	*TLR3*	*USP11*	*ZXDB*
PGBD2	*RAB3GAP1*	*SI*	*STMN1*	*TM4SF18*	*USP12*	*ZZEF1*
PHACTR1	*RANBP17*	*SIN3A*	*STMN2*	*TMCO1*	*USP13*	*ZZZ3*
PHF2	*RAPGEF2*	*SIN3B*	*STMN3*	*TMCO2*	*USP26*	
PIK3CB	*RBM12*	*SIPA1L1*	*STMN4*	*TMEM106B*	*USP31*	
PIK3R1	*RBM27*	*SIX1*	*SULF1*	***TMEM178B***	*USP32*	
PJA1	*RBM28*	*SLC18A1*	*SULF2*	*TMEM2*	*USP34*	
PJA2	*RBMS1*	*SLC26A9*	*SUMO4*	*TMEM57*	*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* isfX1, X2; *ANKRD28* iCRA_g; *C1orf86/FAAP20* tvi4X1,2,3; *DMKN* i5; *FBXO38* iCRA_d; *FKBP7* isf23 AF100751.1; *IGLV10-54* BAA19993.1; *KHDRBS2* iCRA_c; *loc102725117* isf.X1-7; *LRTOMT* isf1c,1a; *MARCH1* ix1; *MASP1* isf1; *MGAM* int iX1; *MTCH1* AAD34059.1; *NTRK3* isof x10, XP_006720612; *PAAAA-AS1* AAV41520.1; *PTPRB* iX5; *PHACTR1* iX6; *RAPGEF2* iX7; *RNF128* isf2; *SH3D19* isfX2,4,5,6,8; *SNAP91* isfD; *TRAJ31,39,43* AAB86765.1, AAB86758.1, AAB86754.1; *VEZF1* iCRA_a,c; *WFDC6* iCRA_a,b; *WDR17* iX5; *XIRP2* 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 ubiquitin conjugation, DNA repair, RNA processing,or pattern recognition response. The relative frequency of appearance of such genes among the N-hCR-bearing genes versus their proportional representation in the human genome remains uncharacterized. CKS2, on a list of genes that are devoid of Asn codons in mammalia, is a paralog of a plasmodium protein (XP_001352106) which has the longest contiguous stretch of 83 Asn residues in plasmodia (382,383). When the plasmodium gene is compared to the human database, the best 3 homologies are to *CKS2, CKS1B* and the N-hCR-bearing-gene $PPP1R13B_{4N\text{-}hCR}$/*ASPP1*, the promoter of which is silenced by methylation in ALL (384). The balance between *CKS2* and *CKS1B* is thought to play a role in multiple cancers (385), including HHV4 associated nasopharyngeal cancer (386) (along with $TRPM7_{4N\text{-}hCR}$). Altered Asn levels could shift the balance between CKS2 and CKS1B to affect cell cycle regulation in multiple cancers including ALL, and, via PPP1R13B, senescence in normal cells (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), *SEPW1* (cell cycle) (391), *TCL1* (leukemia) (392), *CSF3* (innate immunity and aneurysms) (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 plasmodium 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), *MEPC2e1* (109) (A,G,H-hCR), and *HTT* (Q-hCR) (110). The gene list could also extend to *DMPK/SIX5* (111,112), *GCLC* (89), *FMR1* (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 cytostatic 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 neurodysfunction; 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, lipidystrophy, vascular disorders and neurological changes (140-144). $KCNA3_{3N\text{-}hCR}$ 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.* $KCNH4_{3N\text{-}hCR}$ and $KCNH8_{3N\text{-}hCR}$). Pancreatitis and diabetes are associated, respectively, with $CFTR_{4N\text{-}hCR}$ and $SLC26A9_{3N\text{-}hCR}$, 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 $SLC26A9_{3N\text{-}hCR}$) (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 magnesium channels: $TRPM6_{4NhCR}$ and $TRPM7_{3N\text{-}hCR,4NhCR}$. 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 $SLC26A9_{3N\text{-}hCR}$ (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 $SCARB1_{3N\text{-}hCR}$. 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 Ile1145) 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 lippoprotein (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). *SCARB1* affects suseptibility to myocardial infarction (175) and renal cell carcinoma (176,177) activity of lippoprotein 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 suseptibility (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 $F5_{3N\text{-}hCR104t}$ (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. $FGB_{3N\text{-}hCR}$, $GP1BA_{3N\text{-}hCR}$, encoding the platelet membrane receptor (for von Willebrand's factor) associated with ischemic stroke (192), and $CD9_{4N\text{-}hCR}$, 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 $C3_{3N\text{-}hCR}$ (200) to multiple sclerosis through effects on $C7_{3N\text{-}hCR}$ (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 *CLEC6A* (202), *CLEC10A* (203) *CLEC13B*/*LY75*, *MASP1* 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, $PHACTR1_{5N\text{-}hCR}$ 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: $SNCAIP_{5N\text{-}hCR}$ and $ANK3_{5N\text{-}hCR}$. 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 $C1QB_{3N\text{-}hCR}$ (211), or the balance between $C1QL2_{3N\text{-}hCR}$, $C1QL3_{3N\text{-}hCR}$ (212) and $BAI2_{3N\text{-}hCR}$ and their non N-hCR bearing paralogs: *C1QL1* and *BAI3* (213).

Multiple genes encoding N-hCR have been linked to neuropsychiatric disorders, PD, aspects of schizophrenia, Alzheimer's disease, mood disorders [*CDH9* (214), *GTF2I* (215) and *ALDH6A1*], neurological dysfunction (*CDKL5* and *TMEM106B*) (216,217), breast-cancer [*BRCA2*, *CEACAM5*/*CEA* (218), *CYP19A1*/Aromatase (219), *IRS2*, *CLEC10A* (220), *LRP6* and *TBC1D5* (221)], spinal degeneration (*COIL*, *FBXO38*, *ITGAV*, *ASIC2*, *KIAA1217* and *CHAD*), age of onset of amyotrophic lateral sclerosis (ALS) (*TTLL4* and *LAMA3*) (222), dementia in ALS (*TMEM106B*) (223) retinal dystrophy (*TTLL5*) (224), large artery stoke (*TTLL5* and *PHACTR1*) (225) decreased bone density in tamoxifen treated women (*LRP4* and *NCOA1*) (226), ovarian cancer (*TBC1D3* and *TBC1D3F*) (227) T cell anergy (*GRAIL*/*RNF128*/*isf2*) (228-230), asthma, autoimmune diseases, innate immunity (231-233) and the link between innate and adaptive immunity (*FCGR2-A, -B, -C*) (234) suggesting a common etiology of altered Asn homeostasis may need to be considered for some of these conditions.

LRP5, LRP6 and APC are encoded by N-hCR-bearing-genes involved in the Wnt pathway. Rotterlin, which is reported to accelerate the turnover rate of 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 *DZIP1*, *MAML2*, *BOC* and *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 halflife of WNT signalling complexes and the contribution of DSV to turnover of WNT coreceptors FZD and 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 $CPS1_{3N\text{-}hCR}$, regulating the first committed step of urea-cycle entry, and $SLC6A8_{3N\text{-}hCR}$, 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*$_{4N\text{-}hCR}$) (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*$_{3N\text{-}hCR}$ 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 peridontal disease as a diabetes comorbidity through *TMEM178B* or *ANKRD17* in children (252,253); (*cf. LRP1B* and periodontitis in adults) (254). Also affected by *LRP1B* 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. LRP6*) and *PPP1R9A* (*cf. CHRM-2, -3*) (264); bone density by *PHACTR1* (*cf. LRP4, LRP5*); erythropoesis and quality control of mitochondria by *BNIP3L*; nucleic acid processing by *COIL*, *PAPD5*, *THRAP3*, *MEX3B* and *C1orf86/FAAP20*; and diabetes by *THRAP3* (*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*$_{2x3N\text{-}hCR}$ (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 resynthesized once per cell cycle (*cf. COIL* above).

3. Evidence for and against the model, caveats

In vitro translation and in vivo half lifes are consistent with ASNase impaired translocation 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 gaussia 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 translocation 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^{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: periphiral 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 metabolomic 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*$_{3N\text{-}hCR}$ 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).

AAC codons; intrinsically disordered protein assemblies. Most of the poly Asn codon runs reported here consist of the two isoaccepter codons AAT and AAC used in about equal frequency with a slight bias towards homopolymeric runs of AAC. In the gene *IRS2*$_{8N\text{-}hCR}$, 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 homocopolymers encoding poly Q repeats can form triple stranded structures (287), RNA sequences enriched in AAT motifs can be labile (288)]. Interestingly, *PEG10*$_{7N\text{-}hCR}$ and *BNIP3L*$_{5N\text{-}hCR}$ employ AAC codons exclusively in human and mouse (*PEG10*), or in human, mouse, rat, lizard, ~frog 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. *PPP1R9A*$_{5Nx2\text{-}hCR}$, 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 PP1 (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), hepatosplenic lymphoma (298) and regulation of G protein coupled receptor (GPCR) signalling (250). 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.

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.* Taspase1, 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 inflamation. 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 *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 *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 SH2, 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 chemoattractants (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 mTOR1C, 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 metabolomic 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 fluctuations 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 success (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. APOL1, 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), $CHRM3_{3N\text{-}hCR}$ is associated with response to an antidiabetic drug in African Americans (353) (*cf.* $CHRM2_{4N\text{-}hCR}$ 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, ankylosing 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 corneal changes (370), low birth weight (371), diastolic blood pressure (372) rheumatoid arthritis (373), response to haloperidol (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 components, 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 movement 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 fluctuations 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 vestibule residence 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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