

Supplementary Table 1. Proteomic Analysis of Purified NK cells from HESN-PWID Subjects (n=6) compared to Control Donors (n=6). Samples were prepared for label-free quantitative proteomics and sequenced using Gel/LC-MS/MS. The intensity of proteins was normalized relative to the median value for all samples. Fold Change and p-value shown for proteins upregulated or downregulated in HESN-IDU subjects compared to Control donors. S100 protein family members shown in red, IFN-induced proteins shown in blue, and proteins that augment NK cytotoxicity shown in green.

Protein Name (Abbreviation)	Fold Δ	p value	Protein Name (Abbreviation)	Fold Δ	p value
Junction plakoglobin (JUP)	29	0.000298859	Zinc finger protein (ZNF30)	2.3	0.0087842
Plakophilin-1 (PKP1)	16	0.000280363	Prothymosin alpha (PTMA)	2.3	0.037594
Junction plakoglobin (JUP)	12	0.014354935	Heterogenous nucleas ribonucleoprotein L-like (HNRPLL)	2.2	0.0364283
POTE ankyrin domain family member E (POTEE)	10	3.76429 E-07	CCR4 NOT transcription complex subunit 3 (CNOT3)	2.2	0.00016496
Small proline-rich protein 2D (SPRR2D)	9.4	0.040470072	Retinoblastoma-associated protein (RB1)	2.2	0.00602655
S100 protein family member A14 (S100-A14)	9.3	0.001626442	Granzyme H (GZMH)	2.2	0.010411624
S100 protein family member P (S100-P)	8.9	0.017045785	Ceroid-lipofuscinosis (CLN5)	2.2	0.018275059
Desmoplakin (DSP)	8.3	0.014215794	Ena/VASP-like protein (EVL)	2.2	0.001443745
N-sulfoglucosamine sulfohydrolase (Sulfamidase)	7.3	0.015610452	Neutral amino acid transporter A (SLC1A4)	2.2	0.017116421
Calmodulin-like protein 3 (CALML3)	6.9	0.041057192	Protein HIRA (HIRA)	2.2	0.009064615
Uncharacterized protein C1orf21	6.6	0.00348597	DNA topoisomerase 3-beta (TOP3B)	2.2	0.047558523
Tudor domain-containing protein 7 (TDRD7)	6.3	0.049809649	Cytochrome b5 reductase 4 (CYB5R4)	2.1	0.009125014
RasGAP-activating-like protein 1activating-like protein 1 (RASAL1)	5.4	0.034019037	Sentrin-specific protease 3 (SEN3)	2.1	0.032967881
Phosphatase and actin regulator 4 (PHACTR4)	5.3	0.000783258	Early B-cell factor 2 (EBF2)	2.1	0.023893141
Ubiquitin-conjugating enzyme E2 R2 (UBE2R2)	5.0	0.006078517	Bromodomain adjacent to zinc domain 1A (BAZ1A)	2.1	0.035847548
unc-84 homolog B (UNC84B)	5.0	0.02919565	CD44 antigen (CD44)	2.0	0.013280422
Alanine-tRNA ligase (AARS2)	4.9	0.016746157	Heat- and acid- stable phosphoprotein (PDAP1)	2.0	0.018927185
Uncharacterized protein C16orf86	4.6	0.003253033	Leukocyte surface antigen CD53 (CD53)	2.0	0.026441399
dsRNA Sensor 2-5-oligoadenylate synthetase (OASL)	4.4	0.009779752	PTB domain-containing engulfment adapter protein 1 (GULP1)	-2.0	0.04983362
Histidine ammonia-lyase (HAL)	4.3	0.028928842	Ig delta chain C region (IGHD)	-2.0	0.01411930
TatD DNase domain containing 2 (TATDN2)	4.3	0.001303411	Autophagy-related protein 9A (ATG9A)	-2.0	0.03538538
LGALS3 protein variant	4.2	0.003397955	SID1 transmembrane family member 1 (SIDT1)	-2.1	0.03218475
MHC class II antigen (DRB1-13 beta chain)	4.2	0.017679051	Transthyretin (TTR)	-2.1	0.04759216
Cornifin-B (SPRR1B)	4.1	0.038063427	Uncharacterized protein C7orf26 (C7orf26)	-2.1	0.03956630
Aryl hydrocarbon receptor interacting protein (AIP)	3.9	0.039728114	Transmembrane 9 superfamily protein member 2 (TM9SF2)	-2.1	0.01500535
Zinc finger E-box-binding homeobox 2 (ZEB2)	3.9	0.004716317	Inactive tyrosine-protein kinase 7 (PTK7)	-2.1	0.00551808
Ribonucleoside-diphosphate reductase large subunit (RRM1)	3.7	0.000766293	Long-chain-fatty-acid-CoA ligase 1 (ACSL1)	-2.2	0.00706675
Cathepsin H (CTSH)	3.5	0.040865359	Tripartite motif-containing protein 14 (TRIM14)	-2.2	0.00542988
Anchor protein (RESA1)	3.5	0.024684129	Syntaxin-16 (STX16)	-2.2	0.00648326
S100 protein family member A4 (S100-A4)	3.5	0.001349579	Family With Sequence Similarity 114 Member A1 (FAM114A1)	-2.2	0.02143677
Cathepsin B (CTSB)	3.4	0.041705697	Protein phosphatase 1 regulatory subunit 3D (PPP1R3D)	-2.2	0.02674417
Phosphatidylinositol 3-kinase regulatory subunit beta (PIK3R2)	3.3	0.039394839	1-acyl-sn-glycerol-3-phosphate acyltransferase gamma (AGPAT3)	-2.2	0.00247778
Hornerin (HRNR)	3.2	0.007654452	Golgi pH regulator protein (GPR89A;GPR89C)	-2.2	0.04465362
Nuclear factor of activated T-cells, cytoplasmic 3 (NFATC3)	3.2	0.016876239	Integrin-alpha FG-GAP repeat-containing protein 2 (ITFG2)	-2.3	0.01847744
Isoform 2 of Poly [ADP-ribose] polymerase 9 (PARP9)	3.2	0.007129824	Metalloreductase STEAP3 (STEAP3)	-2.3	0.03644999
Phosphoinositide 3-kinase regulatory subunit 5 (PIK3R5)	3.1	0.019367719	Adenosine 3-phospho 5-phosphosulfate transporter 1 (SLC35B2)	-2.4	0.04741338
Carnosine synthase 1 (CARNS1)	3.0	0.022711741	Four and a half LIM domains protein 3 (FHL3)	-2.4	0.01488543
Envoplakin (EVPL)	2.9	0.042477582	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB)	-2.5	0.04314090
GRIP and coiled-coil domain-containing protein 1 (GCC1)	2.9	0.004396623	Insulin-like growth factor-binding protein 2 (IGFBP2)	-2.5	0.04906856
Signal transducer and activator of transcription 1 (STAT1)	2.8	0.001997791	Telomerase Cajal body protein 1 (WRAP53)	-2.6	0.01524567
Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3)	2.8	0.000108398	Membrane-associated phosphatidylinositol transfer protein 2 (PITPNM2)	-2.7	0.01057281
Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1)	2.7	0.006759988	Follistatin-related protein 1 (FSTL1)	-2.9	0.00232623
Carbonyl reductase family member 4 (CBR4)	2.7	0.032304876	Syntaxin 17 (STX17)	-2.9	0.01312083
S100 protein family member A6 (S100-A6)	2.7	0.021541947	CD3 Epsilon Associated Protein (CD3EAP)	-3.0	0.01781196
Nesprin-3 (SYNE3)	2.5	0.040179342	Tumor necrosis factor receptor superfamily member 5 (CD40)	-3.1	0.03249024
Cytochrome c oxidase assembly factor 4 (COA4)	2.5	0.013429178	RNMT-activating mini protein (FAM103A1)	-3.2	0.03481082
CD95 antigen (FAS)	2.5	0.008368771	Coiled-coil domain-containing protein 92 (CCDC92)	-3.8	0.00500800
Absent in melanoma 1 protein (AIM1)	2.5	0.021385575	Zinc finger protein 433 (ZNF433)	-3.8	0.00505429
Interferon gamma-inducible protein 30 (IFI30)	2.4	0.013736473	Angiopietin-1 (ANGPT1)	-4.6	0.03491716
SLIT-ROBO Rho GTPase-activating protein 2 (SRGAP2)	2.4	0.001223446	Sorting nexin-30 (SNX30)	-5.3	0.00009906
Kinesin-like protein (KIF21A)	2.4	0.037986302	Protein tweety homolog 3 (TTYH3)	-5.3	0.00199446
D-3-phosphoglycerate dehydrogenase (PHGDH)	2.3	0.01483779	Protein fem-1 homolog B (FEM1B)	-7.6	0.00172044
Granulysin (GNLY)	2.3	0.019945491	Ubiquinone biosynthesis monooxygenase COQ6 (COQ6)	-11.6	0.03595488
Ubiquitin-like protein ISG15	2.3	0.028520574	MHC class I antigen heavy chain (HLA-A)	-15.8	0.02614281
Carboxylesterase 1 (CES1)	2.3	0.0388884			

Supplementary Table 2. Proteomic Analysis of Purified NK cells from Control Donors (n=2) stimulated for 18 hours with IFN-alpha. Samples were prepared for label-free quantitative proteomics and sequenced using Gel/LC-MS/MS. Fold Change shown for proteins upregulated in IFN-alpha stimulated NK cells compared to unstimulated NK cells from the same donor. IFN-induced proteins shown in blue, and proteins that augment NK cytotoxicity shown in green.

Protein Name (Abbreviation)	Fold Δ
Interferon-induced 17 kDa protein precursor (IFI-17)	9.1
Interferon-induced GTP-binding protein Mx2	7.9
Guanine nucleotide-binding protein G(q) subunit alpha	4.8
NADH dehydrogenase (ubiquinone) complex I, assembly factor 6	4.3
Interferon-stimulated gene 20 kDa protein (ISG-20)	4.1
Signal transducer and activator of transcription 2 (STAT2)	3.9
LOC129607 protein	3.3
Isoform 2 of Chromodomain-helicase-DNA-binding protein 1	3.2
Signal transducer and activator of transcription 1 (STAT1)	2.9
Bone marrow stromal antigen 2 (BST-2/Tetherin)	2.7
UDP-N-acetylhexosamine pyrophosphorylase-like protein 1	2.7
cDNA FLJ36765	2.6
Pleckstrin homology domain containing, family A member 1 (PLEKHA1)	2.6
Werner syndrome protein variant (Fragment)	2.6
Telomeric repeat binding factor (NIMA-interacting) 1 (TERF1)	2.5
Microfibrillar-associated protein 1	2.5
Azurocidin	2.5
Peroxisomal proliferator-activated receptor A-interacting complex 285 kDa	2.4
Cathepsin G (CTSG)	2.3
cDNA FLJ55296,	2.3
N-acetylglucosamine 2-epimerase	2.3
CKLF-like MARVEL transmembrane domain-containing protein 6	2.3
Ubiquitin/ISG15-conjugating enzyme E2 L6	2.3
Isoform 4 of Nucleolar protein 6	2.2
Guanylate-binding protein 4	2.2
Interferon-induced 35 kDa protein (IFI-35)	2.2
Uncharacterized protein	2.2
Interferon-induced, dsRNA-activated protein kinase (PKR)	2.2
Inositol polyphosphate 5-phosphatase K	2.1
DNA-directed RNA polymerase	2.1
dsRNA Sensor 2-5-oligoadenylate synthetase (OASL)	2.1
Lysozyme C precursor	2.0
Thioredoxin domain-containing protein 5 precursor	1.9
mannose-binding 2 (LMAN2), mRNA	1.9
Tripartite motif-containing protein 3 (TRIM-3)	1.9
DMXL1 protein	1.9
Poly [ADP-ribose] polymerase 12	1.9
Neutrophil defensin 3 (HNP-3)	1.9
Bisphosphoglycerate mutase	1.9
Uncharacterized protein C18orf19	1.9
Transcription initiation factor IIE subunit beta	1.9
Protein deltex-3-like	1.8
Protein TFG (Fragment)	1.8
HEAT repeat-containing protein 6	1.8
Pentatricopeptide repeat-containing protein 3	1.8
Isoform H7 of P05164	1.8
Pyruvate dehydrogenase [lipoamide]] kinase isozyme 3	1.8
UPF0598 protein C8orf82	1.7
Replication factor C (activator 1) 5, 36.5kDa (RFC5)	1.7
Importin-11	1.7
HLA class I histocompatibility antigen, alpha chain E (HLA-E)	1.7
Apolipoprotein-L2	1.7
MHC class I antigen	1.6
Guanylate-binding protein 5	1.6