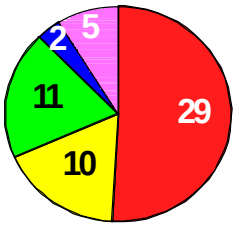
In format provided by Fu *et al.* (doi:10.1038/nri.2016.129)

S1 (Table) | **Human CCCH-Zinc Finger Proteins**

Gene name	Description or other name	Biological Functions	References
CNOT4	CCR4-NOT complex, subunit 4	Megakaryocyte differentiation	1, 2
CPSF4	Cleavage and polyadenylation specific factor 4	Antivirus	3
CPSF4L	Cleavage and polyadnylationspecific factor 4 like	Unknown	
DHX57	Death box protein 57	Unknown	
DUS3l	Dihydrouridine synthase 3-like	Unknown	
HELZ	Helicase with zinc finger domain	Unknown	
HELZ2	Helicase with zinc finger domain 2	Adipocyte differentiation	4
LENG9	Leukocyte receptor cluster member 9	Unknown	
MBNL1	Muscleblind like 1	Myoblast differentiation	5
MBNL2	Muscleblind like 2	Myoblast differentiation	6
MBNL3	Muscleblind like 3	Myoblast differentiation	7
MKRN1	Makorin ring finger protein 1	Tumourigenesis	8
MKRN2	Makorin ring finger protein 2	Neurogenesis	9
MKRN3	Makorin ring finger protein 3	Central precocious puberty	10
NUPL2	Nucleoporin like 2	Unknown	
PAN3	Pab1p-dependent poly(A) nuclease 3	Unknown	
PPP1R10	Protein phosphatase1 regulatory subunit 10	Inhibition of HIV replication	11
PRR3	Proline rich protein 3	Unkonwn	
RC3H1	Roquin-1	Immune homeostasis	12, 13
RC3H2	Roquin-2	Immune homeostasis	14
RNF113A	Ring finger protein 113A	Unknown	
RNF113B	Ring finger protein 113B	Unknown	
TIPARP	TCDD-inducible poly(ADP-ribose) polymerase	Antivirus	15
TOE1	Target of Egr-1	Inhibition of HIV replication	16
TRMT1	TRM1 tRNA methyltransferase 1	Unknown	
U2AF1	U2 small nuclear RNP auxiliary factor, 35 kd subunit	Blood cell differentiation	17
U2AF1L4	U2 small nuclear RNP auxiliary factor 1-like 4	T cell activation	18
ZC3HAV1L	Zinc finger CCCH-type, antiviral 1-like	Unknown	
ZC3H1	Poly(ADP-ribose) polymerase 12	Inflammation, antivirus	19, 20
ZC3H2	Zinc finger CCCH-type antiviral 1	Antivirus	21, 22
ZC3H3	Smad-interacting CPSF-like factor	Unknown	
ZC3H4	Zinc finger CCCH containing 4	Unknown	
ZC3H5	Unkempt homologue	Neuronal differentiation	23
ZC3H5L	Unkempt-like	Unknown	
ZC3H6	Zinc finger CCCH containing 6	Unknown	
ZC3H7A	Zinc finger CCCH containing 7A	Unknown	
ZC3H7B	Zinc finger CCCH containing 7B	Unknown	
ZC3H8	Fetal liver zinc finger protein 1	Thymocyte homeostasis	24
ZC3H9	Zinc finger and G-patch domain-containing protein	Tumor suppressor	25
ZC3H10	Zinc finger CCCH containing 10	Putative tumor suppressor	26
ZC3H11A	Zinc finger CCCH containing 11A	Unknown	
ZC3H12A	MCP-induced protein 1 (MCPIP1), Regnase-1	Inflammation and immunity	27, 28, 29
ZC3H12B	MCP-induced protein 2 (MCPIP2)	Unknown	
ZC3H12C	MCP-induced protein 3 (MCPIP3)	Inflammation	30
ZC3H12D	MCP-induced protein 4 (MCPIP4)	Inflammation and immunity	31, 32
ZC3H13	Zinc finger CCCH containing 13	Inflammation	33
ZC3H14	Nab2 homologue	Neuron differentiation	34
ZC3H15	Immediate early response erythropoietin 4 (LEREPO4)	HIV replication	35
ZC3H16	RNA binding motif protein 22 (RBM22)	Unknown	
ZC3H17	RNA binding motif protein 26 (RBM26)	Unknown	
ZC3H18	Conserved nuclear protein Nhn1	Inflammation	33
ZC3H19	Zinc finger, Matrin type 5 (ZMAT5)	Unknown	
ZC3H20	RNA binding motif protein 27 (RBM27)	Unknown	
ZC3H22	U2AF1-related sequence 2 (ZRSR2)	Blood cell differentiation	36
ZFP36	Tristetraprolin (TTP), TIS11	Inflammation and immunity	37, 38
ZFP36L1	Zinc finger protein 36-like 1, TIS11B	Immune cell maturation	39
ZFP36L2	Zinc finger protein 36-like 2, TIS11D	Immune cell maturation	39

In format provided by Fu *et al.* (doi:10.1038/nri.2016.129)

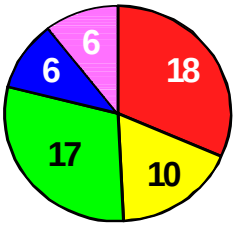
a



CCCH-zinc finger numbers

1 CCCH-ZF			2 CCCH-ZF	3 CCCH-ZF		4 CCCH-ZF	5 CCCH-ZF
CNOT4	RC3H1	ZC3H12C	MBNL1	MKRN1	ZC3H11A	CPSF4L	CPSF4
DHX57	RC3H2	ZC3H12D	MBNL3	MKRN3		MBNL2	ZC3H3
DUS3L	RNF113A	ZC3H13	MKRN2	ZC3H1			ZC3H5
HELZ	RNF113B	ZC3H15	U2AF1	ZC3H2			ZC3H5L
HELZ2	TIPARP	ZC3H16	U2AF1L4	ZC3H4			ZC3H14
LENG9	TOE1	ZC3H17	ZC3HAV1L	ZC3H6			
NUPL2	TRMT1	ZC3H18	ZC3H22	ZC3H7A			
PAN3	ZC3H9	ZC3H19	ZFP36	ZC3H7B			
PPP1R10	ZC3H12A	ZC3H20	ZFP36L1	ZC3H8			
PRR3	ZC3H12B		ZFP36L2	ZC3H10			

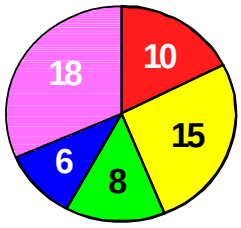
b



CCCH-zinc finger types

$C\text{-}X_8\text{-}C\text{-}X_5\text{-}C\text{-}X_3\text{-}H$		$C\text{-}X_7\text{-}C\text{-}X_5\text{-}C\text{-}X_3\text{-}H$		$C\text{-}X_{7\text{-}9}\text{-}C\text{-}X_{4\text{-}6}\text{-}C\text{-}X_3\text{-}H$		$C\text{-}X_5\text{-}C\text{-}X_5\text{-}C\text{-}X_3\text{-}H$	Others
HELZ	U2AF1	DHX57	ZC3H18	CNOT4	ZC3H4	HELZ2	DUS3L
PAN3	U2AF1L4	LENG9		CPSF4	ZC3H6	ZC3H12A	ZC3HAV1L
PPP1R10	ZC3H13	MKRN1		CPSF4L	ZC3H7A	ZC3H12B	ZC3H1
PRR3	ZC3H17	NUPL2		MBNL1	ZC3H7B	ZC3H12C	ZC3H2
RC3H1	ZC3H19	TIPARP		MBNL2	ZC3H8	ZC3H12D	ZC3H5
RC3H2	ZC3H20	TRMT1		MBNL3	ZC3H10	ZC3H14	ZC3H5L
RNF113A	ZFP36	ZC3H9		MKRN2	ZC3H11A		
RNF113B	ZFP36L1	ZC3H15		MKRN3	ZC3H22		
TOE1	ZFP36L2	ZC3H16		ZC3H3			

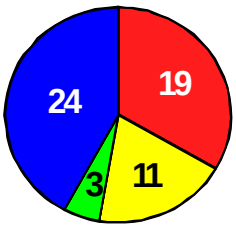
c



Molecular functions

mRNA splicing		mRNA decay		Other RNA metabolism	Others	Not determined	
CPSF4	ZC3H22	CNOT4	ZC3H12C	HELZ	MKRN1	CPSF4L	ZC3H5L
MBNL1		PAN3	ZC3H12D	HELZ2	MKRN2	DHX57	ZC3H6
MBNL2		RC3H1	ZC3H14	NUPL2	MKRN3	DUS3L	ZC3H7A
MBNL3		RC3H2	ZFP36	TRMT1	PPP1R10	LENG9	ZC3H7B
TIPARP		TOE1	ZFP36L1	ZC3H1	ZC3H8	RNF113A	ZC3H10
U2AF1		ZC3H2	ZFP36L1	ZC3H5	ZC3H9	RNF113B	ZC3H15
U2AF1L4		ZC3H3		ZC3H11A		PRR3	ZC3H17
ZC3H13		ZC3H12A		ZC3H18		ZC3HAV1L	ZC3H19
ZC3H16		ZC3H12B				ZC3H4	ZC3H20

d



Biological functions

Immune regulation & antivirus			Differentiation		Cancers	Unknown		
CPSF4	ZC3H2	ZFP36	CNOT4	ZC3H5	MKRN1	CPSF4L	RNF113A	ZC3H7A
PPP1R10	ZC3H8	ZFP36L1	HELZ2	ZC3H14	ZC3H9	DHX57	RNF113B	ZC3H7B
RC3H1	ZC3H12A	ZFP36L2	MBNL1	ZC3H22	ZCH10	DUS3L	TRMT1	ZC3H11A
RC3H2	ZC3H12C		MBNL2			HELZ	ZC3HAV1L	ZC3H12B
TIPARP	ZC3H12D		MBNL3			LENG9	ZC3H3	ZC3H16
TOE1	ZC3H13		MKRN2			NUPL2	ZC3H4	ZC3H17
U2AF1L4	ZC3H15		MKRN3			PAN3	ZC3H5L	ZC3H19
ZC3H1	ZC3H18		U2AF1			PRR3	ZC3H6	ZC3H20

S2 | Categories of human CCCH-zinc finger proteins. a | Categories of CCCH-zinc finger proteins divided by CCCH-zinc finger numbers. Most of proteins contain 1-3 CCCH-zinc fingers (49 among 57), a few of proteins contain 4-5 CCCH-zinc fingers (7 among 57). It is to note that several human proteins such as ZC3H5 contain different numbers of CCCH-zinc fingers with their mouse counterparts. **b |** Categories of CCCH-zinc finger proteins divided by CCCH-zinc finger types. Most of CCCH-zinc finger proteins contains C-X7-9-C-X4-6-C-X3-H class zinc fingers (45 among 57), Several proteins including ZC3H12 family, ZC3H14 and HELZ2 containing a single C-X5-C-X5-C-X3-H type zinc finger. **c |** Categories of CCCH-zinc finger proteins divided by molecular function. Most of CCCH-zinc finger proteins involved in the regulation of RNA metabolism including RNA splicing, polyadenylation, export, translation and decay (33 among 57). Others act as transcriptional repressors or signal transducers. The molecular functions of 18 CCCH-zinc finger proteins are not yet determined. **d |** Categories of CCCH-zinc finger proteins divided by biological function. Though the biological functions of 24 CCCH-zinc proteins are not characterized, the other proteins are crucial in the regulation of immune response, cell differentiation and cancer cell growth.

In format provided by Fu *et al.* (doi:10.1038/nri.2016.129)

S3 BOX. Antiviral function of CCCH zinc finger proteins

Several CCCH-zinc finger proteins exert antiviral functions, with mechanisms including degradation of viral RNA, repression of viral RNA translation, and enhancing antiviral signaling. For example, ZAP, also known as PARP13, ZC3H2 or ZC3HAV1, is a broad-spectrum antiviral protein that targets different viral families such as retroviruses, alpha viruses, filoviruses, and hepadna viruses[1]. ZAP targets specific viral RNAs for decay and translational repression by recruiting destabilizing factors and other effector proteins[2, 3]. Interestingly, ZAPS, a short splicing isoform of ZAP without a PARP domain, functions as a potent stimulator of interferon responses in human cells, mediated by the RNA helicase RIG-I. ZAPS was shown to associate with RIG-1 and promote the oligomerization and ATPase activity of RIG-I, which led to robust activation of IRF3 and the NF-κB transcription factor. Disruption of the gene encoding ZAPS resulted in impaired induction of IFNα, INFβ and other cytokines after viral infection. These results indicate that ZAPS is a key regulator of RIG-I signaling during the innate antiviral immune response[4]. Two other PARP-containing proteins, PARP12 and TIPARP, also belong to the CCCH-zinc finger protein superfamily and are essential for an effective antiviral innate immune response[5, 6].

Besides critically regulating innate and adaptive immune responses, MCPIP1 also exhibits broad-spectrum antiviral effects through viral RNA binding and degradation. MCPIP1 can target viruses from several different families, including JEV, DEN-2, HIV and HCV[7-9]. Interestingly, TTP has also been shown to inhibit HIV-1 production by binding to viral genomic RNA and promoting its decay[10]. TOE1 (target of Egr-1), also a CCCH-zinc finger protein, displays deadenylase activity in cultured cells and is involved in mRNA splicing. Interestingly, a recent study revealed that TOE1 can be secreted from activated $CD8^+$ T cells and enter $CD4^+$ T cells, where it can inhibit HIV-1 replication by binding to TAR sequences and repressing its transcription[11].

1. Todorova, T., Bock, F.J., Chang, P. Poly(ADP-ribose) polymerase-13 and RNA regulation in immunity and cancer. *Trends Mol. Med*. **21**, 373-384 (2015).
2. Guo, X., Ma, J., Sun, J., Gao, G. The zinc-finger antiviral protein recruits the RNA processing exosome to degrade the target mRNA. *Proc. Natl. Acad. Sci. USA*. **104**, 151-156 (2007).
3. Zhu, Y., Wang, X., Goff, S.P., Gao, G. Translational repression precedes and is required for ZAP-mediated mRNA decay. *EMBO J*. **31**, 4236-4246 (2012).
4. Hayakawa, S. et al. ZAPS is a potent stimulator of signaling mediated by the RNA helicase RIG-I during antiviral responses. *Nat. Immunol*. **12**, 37-44 (2011).
5. Atasheva, S., Frolova, E.I., Frolov, I. Interferon-stimulated poly(ADP-Ribose) polymerases are potent inhibitors of cellular translation and virus replication. *J. Virol*. **88**, 2116-2130 (2014).
6. Welsby, I. et al. PARP12, an interferon-stimulated gene involved in the control of protein translation and inflammation. *J. Biol. Chem*. 289, 26642-26657 (2014).
7. Lin, R.J. et al. MCPIP1 ribonuclease exhibits broad-spectrum antiviral effects through viral RNA binding and degradation. *Nucleic Acids Res*. **41**, 3314-3326 (2013).
8. Liu, S. et al. MCPIP1 restricts HIV infection and is rapidly degraded in activated CD4+ T cells. *Proc. Natl. Acad. Sci. USA.* **110**, 19083-19088 (2013).
9. Lin, R.J. et al. MCPIP1 suppresses hepatitis C virus replication and negatively regulates virus-induced proinflammatory cytokine responses. *J. Immunol*. **193**, 4159-4168 (2014).
10. Maeda M, et al. Tristetraprolin inhibits HIV-1 production by binding to genomic RNA. *Microbes Infect*. **8**, 2647-2656 (2006).
11. Sperandio, S. et al. TOE1 is an inhibitor of HIV-1 replication with cell-penetrating capability. *Proc. Natl. Acad. Sci. USA.* **112**, E3392-3401 (2015).

References for S1

1. Albert, T.K., et al. Identification of a ubiquitin-protein ligase subunit within the CCR4-NOT transcription repressor complex. *EMBO J*. **21**, 355-364 (2002).
2. Zhang, L., *et al*. Cross-talk between PRMT1-mediated methylation and ubiquitylation on RBM15 controls RNA splicing. *Elife.* **4** (2015).
3. Twu, K.Y., Noah, D.L., Rao, P., Kuo, R.L., Krug, R.M. The CPSF30 binding site on the NS1A protein of influenza A virus is a potential antiviral target. *J. Virol*. **80**:3957-3965 (2006).
4. Katano-Toki, A., *et al*.THRAP3 interacts with HELZ2 and plays a novel role in adipocyte differentiation. *Mol. Endocrinol.* **27**:769-780 (2013).
5. Kanadia, R.N., *et al*. A muscleblind knockout model for myotonic dystrophy. *Science*. **302**:1978-1980 (2003).
6. Hao, M., *et al.* Muscleblind-like 2 (Mbnl2) -deficient mice as a model for myotonic dystrophy. *Dev. Dyn*. **237**:403-410 (2008).
7. Lee, K.S., *et al*. RNA-binding protein Muscleblind-like 3 (MBNL3) disrupts myocyte enhancer factor 2 (Mef2) {beta}-exon splicing. *J. Biol. Chem*. **285**:33779-33787 (2010).
8. Lee, E.W., *et al*. Differential regulation of p53 and p21 by MKRN1 E3 ligase controls cell cycle arrest and apoptosis. *EMBO J*. **28**:2100-2113 (2009).
9. Yang, P.H., *et al.* Makorin-2 is a neurogenesis inhibitor downstream of phosphatidylinositol 3-kinase/Akt (PI3K/Akt) signal. *J Biol Chem*. **283**:8486-8495 (2008).
10. Abreu, A.P., et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. *N. Engl. J. Med*. **368**:2467-2475 (2013).
11. Kapoor, R., *et al*. The miRNA miR-34a enhances HIV-1 replication by targeting PNUTS/PPP1R10, which negatively regulates HIV-1 transcriptional complex formation. *Biochem. J.* **470**:293-302 (2015).
12. Vinuesa, C.G. *et al*. A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity. *Nature.* **435**, 452-458 (2005).
13. Yu, D. *et al*. Roquin represses autoimmunity by limiting inducible T-cell co-stimulator messenger RNA. *Nature*. **450**, 299-303 (2007).
14. Pratama, A. *et al*. Roquin-2 shares functions with its paralog Roquin-1 in the repression of mRNAs controlling T follicular helper cells and systemic inflammation. *Immunity.* **38**, 669-680 (2013).
15. Atasheva, S., Frolova, E.I., Frolov, I. Interferon-stimulated poly(ADP-Ribose) polymerases are potent inhibitors of cellular translation and virus replication. *J. Virol*. **88**(4):2116-2130 (2014).
16. Sperandio, S. *et al*. TOE1 is an inhibitor of HIV-1 replication with cell-penetrating capability. *Proc. Natl. Acad. Sci. USA*. **112**, E3392-3401 (2015).
17. Yoshida, K., *et al*. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature*. **478**:64-69 (2011).
18. Heyd, F., ten Dam, G., Möröy, T. Auxiliary splice factor U2AF26 and transcription factor Gfi1 cooperate directly in regulating CD45 alternative splicing. *Nat. Immunol*. **7**, 859-867 (2006).
19. Atasheva, S., Frolova, E.I., Frolov, I. Interferon-stimulated poly(ADP-Ribose) polymerases are potent inhibitors of cellular translation and virus replication. *J. Virol*. **88**, 2116-2130 (2014).
20. Welsby, I. *et al*. PARP12, an interferon-stimulated gene involved in the control of protein translation and inflammation. *J. Biol. Chem.* **289**, 26642-26657 (2014).

21. Guo, X., Ma, J., Sun, J., Gao, G. The zinc-finger antiviral protein recruits the RNA processing exosome to degrade the target mRNA. *Proc. Natl. Acad. Sci. USA*. **104**, 151-156 (2007).
22. Zhu, Y., Wang, X., Goff, S.P., Gao, G. Translational repression precedes and is required for ZAP-mediated mRNA decay. *EMBO J*. **31**, 4236-4246 (2012).
23. Avet-Rochex, A., *et al.* Unkempt is negatively regulated by mTOR and uncouples neuronal differentiation from growth control. *PLoS Genet.* **10**:e1004624 (2014).
24. Hwang, E.S., Ho, I.C. Regulation of thymocyte homeostasis by Fliz1. *Immunology.* **106**, 464-469 (2002).
25. Ordway, J.M., *et al*. Comprehensive DNA methylation profiling in a human cancer genome identifies novel epigenetic targets. *Carcinogenesis*. **27**:2409-2423 (2006).
26. Guardiola-Serrano, F., *et al*. Gene trapping identifies a putative tumor suppressor and a new inducer of cell migration. *Biochem. Biophys. Res. Commun*. **376**:748-752 (2008).
27. Liang, J. *et al*. A novel CCCH-zinc finger protein family regulates proinflammatory activation of macrophages. *J. Biol. Chem*. **283**, 6337-6346 (2008).
28. Matsushita, K. et al. Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. *Nature*. **458**, 1185-1190 (2009).
29. Liu, S. *et al*. MCPIP1 restricts HIV infection and is rapidly degraded in activated CD4+ T cells. Proc Natl Acad Sci U S A. **110**, 19083-19088 (2013).
30. Liu, L., *et al*. Zc3h12c inhibits vascular inflammation by repressing NF-κB activation and pro-inflammatory gene expression in endothelial cells. *Biochem. J*. **451**:55-60 (2013).
31. Zhang, H. *et al*. ZC3H12D attenuated inflammation responses by reducing mRNA stability of proinflammatory genes. *Mol Immunol*. **67**, 206-212 (2015).
32. Minagawa, K. *et al*. Posttranscriptional modulation of cytokine production in T cells for the regulation of excessive inflammation by TFL. *J. Immunol*. **192**, 1512-1524 (2014).
33. Gewurz, B.E., *et al*. Genome-wide siRNA screen for mediators of NF-κB activation. Proc. Natl. Acad. Sci. USA. **109**:2467-2472 (2012).
34. Pak, C., *et al*. Mutation of the conserved polyadenosine RNA binding protein, ZC3H14/dNab2, impairs neural function in Drosophila and humans. Proc. Natl. Acad. Sci. USA. **108**:12390-12395 (2011).
35. Capalbo, G., *et al*. Inhibition of X4-tropic HIV type 1 replication by knockdown of the cellular protein LEREPO4. *AIDS Res. Hum. Retroviruses*. **26**:1155-1161 (2010).
36. Thol, F., *et al*. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplasticsyndromes. *Blood*. **119**:3578-3584 (2012).
37. Carballo, E., Lai, W.S., Blackshear, P.J. Feedback inhibition of macrophage tumor necrosis factor-alpha production by tristetraprolin. *Science*. **281**, 1001-1005 (1998).
38. Taylor, G.A. *et al*. A pathogenetic role for TNF alpha in the syndrome of cachexia, arthritis, and autoimmunity resulting from tristetraprolin (TTP) deficiency. *Immunity*. **4**, 445-454 (1996).
39. Hodson, D.J. *et al*. Deletion of the RNA-binding proteins ZFP36L1 and ZFP36L2 leads to perturbed thymic development and T lymphoblastic leukemia. *Nat. Immunol*. **11**, 717-724 (2010).