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Renaming the *DSCR1/Adapt78* gene family as *RCAN*: regulators of calcineurin

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INTRODUCTION AND SIGNIFICANCE

The serine-threonine phosphatase, calcineurin (also known as PP3C, formerly PP2B) plays pivotal roles in a wide series of key biological processes. A new family of regulators of calcineurin (RCANs) has been shown to modulate calcineurin activity under physiological and pathological conditions. Unfortunately, the members of this family have been given some 20 different names over the past 10 years largely because their

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function as calcineurin regulators was discovered only recently. These diverse names have resulted in great confusion, and still represent a barrier to advancement in the field. In writing this paper, our goals were *1)* to bring together all the previous names for members of this RCAN family in one publication, where their identities can be easily compared; *2)* to introduce RCAN as a rational, functional name for this gene family; and *3)* to propose a coherent nomenclature system for the known RCAN family members, as well as additional ones that may be found in the future.

PROPOSAL

In the interest of advancing work in the field, we propose a unified nomenclature for the family of genes related to the locus initially designated as human *DSCR1*. The new *RCAN* nomenclature has been approved by both the HUGO Gene Nomenclature Committee (HGNC) and the Mouse Genomic Nomenclature Committee (MGNC). Homologs, orthologs, and paralogs of this gene, and their protein products, should now be named "regulators of calcineurin" to reflect the ability of most family members to bind and regulate the protein phosphatase enzyme, calcineurin (see **Table 1**). The gene names would be abbreviated as *RCAN* (*Rcan* for mouse and rat) and their protein products as RCAN (Rcan for rat and mouse). The original *DSCR1* locus on human chromosome 21 would be designated *RCAN1*. Because all yeast and fungal genes and proteins are named with only three letters and usually a number, regulators of the calcineurin genes would be referred to as *RCN1*, and the proteins as RCN1, in these species.

The *RCAN1* gene consists of seven exons, of which exons 1–4 can be alternatively transcribed or spliced to produce different mRNA isoforms. In the new nomenclature, two identified RCAN1 protein isoforms would be designated RCAN1–1 and RCAN1–4 (see **Fig. 1**). Similarly, the homologous gene locus on human chromosome 6 would be designated *RCAN2* (protein isoforms RCAN2–3 and RCAN2–4). The family member on human chromosome 1 would be designated *RCAN3*. Orthologs from other mammalian species would follow the same numbering scheme based on their relative identity to these three human family members. Structural homologues from species containing only one *RCAN* family member would be named simply *RCAN1*, with additional numbered genes added if new loci are identified. When conversing, RCAN may be easily referred to as "R-can" (pronounced "ar-can"). This new naming system provides information regarding an important function of the RCAN genes and proteins, and will make it much easier for outside researchers to access the literature and grasp the potential importance of these highly conserved regulators of calcineurin signaling.

TABLE 1. *A historical overview of the existing RCAN gene nomenclature*

Name	Source	Reference	Year
The *RCAN1* gene			
DSCR1	*Homo sapiens*	(1)	1995
	Saccharomyces cerevisiae	(2)	2000
	Caenorhabditis elegans	(2)	2000
Dscr1	*Mus musculus*	(3)	2000
Adapt78	*Cricetulus griseus*	(4)	1997
	Homo sapiens	(5)	2001
MCIP1	*Mus musculus*	(6)	2000
	Homo sapiens	(6)	2000
Calcipressin1 [Csp1,CALP1]	*Homo sapiens*	(7) [(8, 9)]	2000 [2003, 2003]
RCN1, Rcn1p	*Saccharomyces cerevisiae*	(10)	2000
CBP1	*Cryptococcus neoformans*	(11)	2000
RCN-1	*Caenorhabditis elegans*	(12)	2003
Nebula (nla)	*Drosophila melanogaster*	(13)	2003
Sarah (sra)	*Drosophila melanogaster*	(14)	2004
RCAN1	*Homo sapiens*	(15)	2005
The *RCAN2* gene			
ZAKI-4	*Homo sapiens*	(16)	1996
Dscr1l1	*Mus musculus*	(2, 3)	2000
MCIP2	*Mus musculus*	(17)	2000
Calcipressin 2	*Mus musculus*	(18)	2006
The *RCAN3* gene			
DSCR1L2	*Homo sapiens*	(2)	2000
Dscr1l2	*Mus musculus*	(3)	2000
RCAN3	*Homo sapiens*	(19)	2007

Table 1 is an attempt to bring together all the published names for the *RCAN* family of genes to demonstrate the relationships between family members. Only the first published use of a name (to the best of our knowledge) is referenced in each species or genus. The [Csp1,CALP1] variations on calcipressin 1 (and their references) appear in brackets to indicate they were modifications of an existing proposed name.

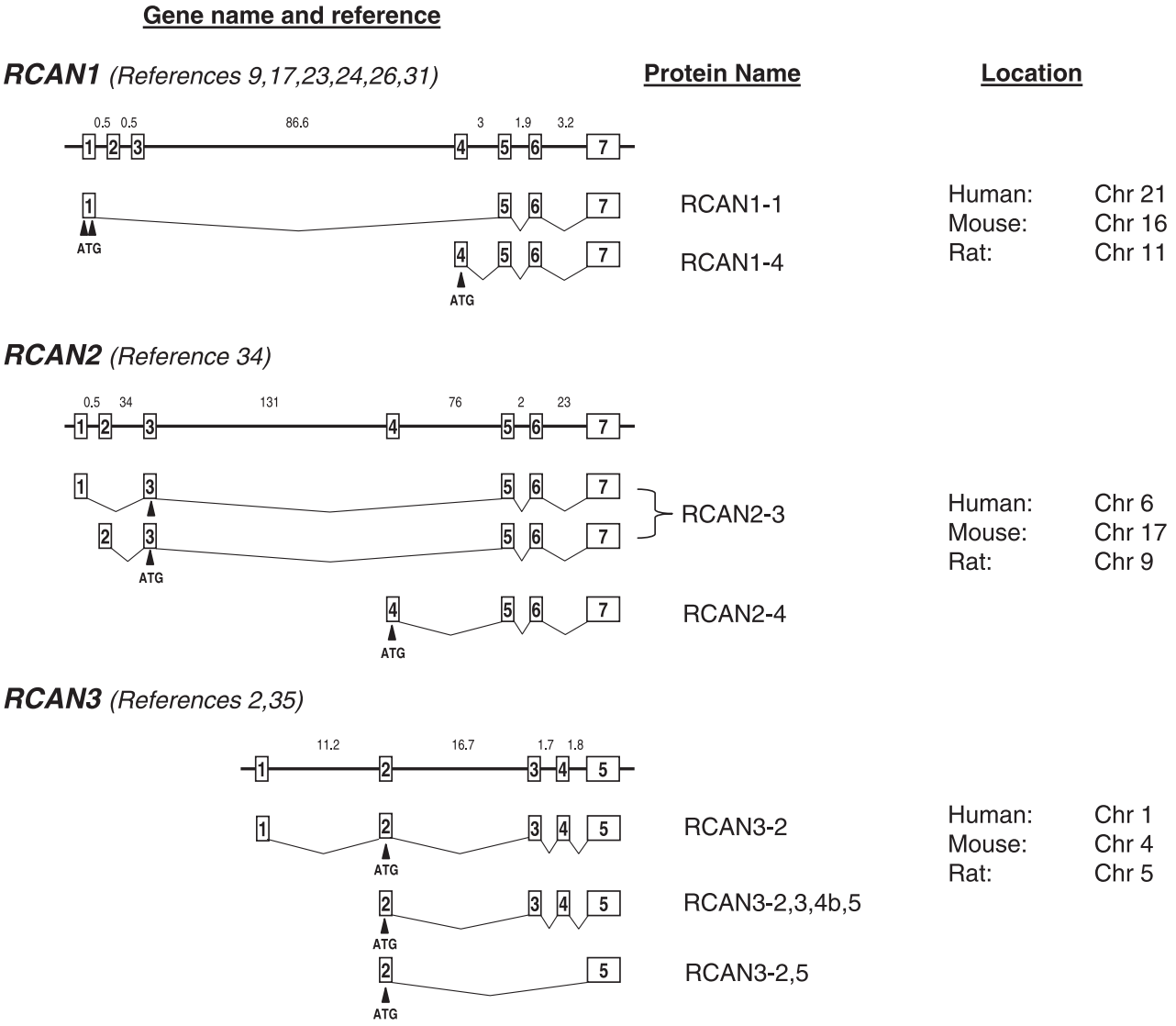

Figure 1. The intron/exon structure, transcripts, and protein products of the human *RCAN* genes. Overall: Note that all structures, exon locations, and protein isoform nomenclature are based on that of the human RCAN1 gene. Genomic distances between exons (*i.e.*, intron sizes) are given in kilobases. RCAN1: Protein isoforms have been named based on the (human) exon location of the translation start site. In the new nomenclature, the various *RCAN1* transcripts corresponding to alternative first exons would be designated *RCAN1–1, RCAN1–2, etc.*, as previously proposed (31). Exons 5, 6, 7 are omitted from the mRNA transcript and protein isoform nomenclature above. This is possible since exons 5, 6, 7 are invariant components of all transcripts so far observed. The transcript encoding RCAN1–1 starts at exon 1 and its expression is stimulated by glucocorticoids. The transcript encoding RCAN1–4 begins at exon 4 and its expression is controlled by oxidative stress, calcium, and calcineurin. One long (RCAN1–1L) and one short (RCAN1–1S) version of the RCAN1–1 protein are generated due to alternative translation initiation sites in the *RCAN1–1* transcript. RCAN2: the system of nomenclature used for each mRNA transcript and protein isoform is the same as that proposed for RCAN1. The *RCAN2–1,3* and *RCAN2–2,3* transcripts both produce the same protein: RCAN2–3. This is because the first initiation codon lies within exon 3. It should be noted that *RCAN2–4* (but not *RCAN2–1,3* or *RCAN2–2,3*) is up-regulated by the thyroid hormone. RCAN3: the system of nomenclature used for each mRNA transcript and protein isoform is similar to that proposed for RCAN1. Exon 4b (an exon 4 variant lacking the first 30 bases, leading to a product lacking 10 amino acids) makes it necessary to specify the particular exon included in the *RCAN3–4b* mRNA isoform. Exon 1 has been redefined as described by Canaider *et al.* (35); the first initiation codon lies within exon 2. The originally published name for *RCAN3–2,5* was *DSCR1L2-E2E5* (35), and it has been reported that proteins encoded by these mRNA transcripts interact with cardiac troponin I (TNNI3) (35) and calcineurin (19).

THE *RCAN* GENE FAMILY

DSCR1/RCAN1 was first identified by the group of Estivill as an expressed sequence on a YAC clone from human chromosome 21 (1). The YAC clone contained a portion of the chromosome known as the Down syndrome critical region (DSCR) (20, 21). Thus, the name "Down syndrome candidate region 1" gene (originally designated "critical region 1" gene), abbreviated as *DSCR1,* was used for the first previously unidentified gene on this YAC clone. Although we are suggesting a new function-based nomenclature, the relationship of

RCAN1/DSCR1 to human Down syndrome still appears strong. Other open reading frames identified from this region became designated as *DSCR 2/3/4* (or A/B/C), *etc.*, in the literature until functional data could be linked with their respective activities. Two major protein isoforms of 252 (RCAN1–1) and 197 (RCAN1–4) amino acids are expressed from the *RCAN1* gene by alternative promoter usage and first exon choice in humans and the mouse (9, 22–24). The proximal promoter controlling expression of RCAN1–4 is activated by calcineurin-NFAT signaling (17) in response to different stimuli such as VEGF (25, 26) and depolarization in neurons (27), among others. The distal promoter (RCAN1–1) is activated by glucocorticoids (28) and down-regulated by Notch-dependent signaling (29).

Important insights into the regulation and function of *RCAN1/DSCR1/Adapt78* came when the Davies laboratory demonstrated that its expression was transiently induced during cellular adaptation to oxidative stress and calcium stress (4). They named the gene *Adapt78* and went on to show that it is an oxidant stress response gene and a calcium stress response gene that can protect cells from various forms of stress (30, 31). A critical breakthrough came when it was demonstrated that the protein could bind to and inhibit the calcium-regulated protein phosphatase calcineurin in yeast (10), mouse (6), human (7), and *Cryptococcus neoformans* (11). The yeast homologue was named *RCN1* for "regulator of calcineurin 1" (10). The mouse ortholog was officially designated *Dscr1* (22), but its protein product was published as MCIP1 (6) for "myocyte-enriched calcineurin-interacting protein 1" and later "modulatory calcineurin interacting protein" (32). The gene from *C. neoformans* was named *CBP1* for calcineurin binding protein 1 (11). The *Drosophila* homologue has been published with a variety of names, including *NEBULA* (*nla*) for the gene (13) and sarah (sra) for the protein (14). The *Caenorhabditis elegans* gene has been named *RCN-1* (12).

The human *RCAN2* locus was first published as *ZAKI-4* (16), a gene whose expression was induced in response to thyroid hormone. *ZAKI-4* was later designated *DSCR1L1* for "*DSCR1*-like protein 1" (2). As shown in Fig. 1, three transcripts (*RCAN2–1,3, RCAN2–2,3*, and *RCAN2–4*) and two protein products (RCAN2–3 and RCAN2–4) have been identified (33). It has also been noted that the RCAN2–4 protein isoform is up-regulated by thyroid hormone (33) *via* an AKT/PKB-dependent signaling pathway (34). The *RCAN3* gene was identified on the basis of its sequence similarity to *RCAN1* and *RCAN2*, and was named *DSCR1L2* (2). Alternatively spliced *RCAN3* isoforms have also been described (2, 35). *MCIP 1, 2*, and *3* standing for "modulatory calcineurin-interacting proteins" were also suggested as a naming scheme for the three mammalian genes (32, 36).

This multiplicity of gene and protein names (see Table 1) is awkward and highly confusing to those outside the field. The earlier names also provide no functional information and are difficult to apply to genes from diverse species. Based on its ability to inhibit calcineurin, the term "calcipressin" has been suggested (7, 11), and has been abbreviated in a variety of ways, including *Csp* (8) and *CALP* (9). More recently, however, it was demonstrated that RCAN1 protein appears to be capable of either inhibiting or facilitating calcineurin signaling depending on the context (36–38). Thus, the name "calcipressin 1" may not accurately reflect the full biological functions of these proteins. Furthermore, the similarity of the name calcipressin to the calcium binding proteins calretinin, calbindin, and calsequestrein implies calcium binding properties, yet there is no evidence that RCANs bind calcium. Therefore, the former designations all seem inadequate when compared with RCAN.

REGULATION OF CALCINEURIN BY RCANs

Several laboratories have reported that animal and fungal RCAN1 and RCAN2 can specifically bind to and down-regulate the activity of calcineurin (6, 7, 10, 11, 33). Calcineurin is a protein phosphatase enzyme composed of calcineurin A (CnA) and calcineurin B (CnB) subunits. The CnA subunit has a catalytic domain, a CnB binding domain, and a C-terminal regulatory domain. In the absence of calcium, the protein phosphatase calcineurin is inactive because of a C-terminal autoinhibitory domain ("AID") that blocks the active site in the catalytic CnA subunit. The binding of a calcium/calmodulin complex causes a conformational change that removes the AID, thus "activating" the protein phosphatase activity.

It has been shown that RCAN1 and RCAN2 bind calcineurin at or near the catalytic domain of CnA (6, 7, 10). The primary calcineurin binding portion of the RCAN1 protein is encoded by exon 7 (7, 39), which is common to all RCAN1 isoforms. This region includes two RCAN1 sites of interaction with calcineurin. One is a PxIxxT motif that resembles a PxIxIT calcineurin-interacting sequence found in NFAT proteins (40). The second is an ELHA motif that binds to calcineurin but may need to be in a wider amino acid context, such as the CIC motif, in order to inhibit calcineurin (41). Two additional sites for calcineurin interaction have been reported. One is specific to the N-terminal region of RCAN1–4 (42). The other is the highly conserved serine-proline (SP) motif (known also as a FLISPP motif), which is a calcineurin substrate. It has been demonstrated, however, that the SP motif is neither sufficient nor required for the inhibition of calcineurin, although it can act as a competitive inhibitor (9, 38, 39, 41, 42). The state of phosphorylation of the RCAN1 SP motif correlates with the protein half-life (9). RCAN binding to calcineurin does not interfere with binding of either the calcium/calmodulin complex or the regulatory B subunit to the catalytic A subunit of calcineurin. In fact, most data indicate that RCAN1 and RCAN2 bind preferentially to the activated form of calcineurin, suggesting that calcium/calmodu-

lin binding facilitates RCAN binding by removing the AID to expose the catalytic domain.

There are ample data indicating that RCAN1 and RCAN2 can bind calcineurin and that increased RCAN levels can inhibit calcineurin's protein phosphatase activity. Nevertheless, some of the phenotypes observed in yeast, *C. neoformans* (43), and mouse mutants lacking RCAN1 or RCAN2 are similar to those observed in mutants lacking calcineurin (18, 36). This suggests that RCANs may also be required for proper calcineurin signaling. There is genetic evidence from yeast indicating that phosphorylation of the conserved serine 108 of RCAN-1–4 by GSK-3 may release the inhibitory activity of RCAN and somehow facilitate calcineurin signaling (37). Similar results have been reported in fungi (43) and mammals (44). Although the exact mechanism of this process is not known, it has been suggested that GSK-3-phosphorylated RCAN may act on calcineurin in a manner similar to the chaperoning properties of phosphorylated inhibitor-2, relative to the protein phosphatase PP1 (37). In the case of mammalian RCAN1, the switch seems to depend on 14–3-3 binding (44). RCAN3 (formerly DSCR1L2) has been shown to bind cardiac troponin I (TNNI3) (35), and very recently evidence was presented that it also binds calcineurin and inhibits NFAT-dependent gene expression (19).

RATIONALE FOR ACCEPTANCE OF A COMMON NAME

Laboratories around the globe are now studying *RCAN* genes and their protein products. RCAN1 has been shown to inhibit cardiac hypertrophy (45), to attenuate angiogenesis and cancer (26), and to be associated with Down syndrome and Alzheimer disease (5, 7, 24, 46–50). RCAN1-dependent inhibition of calcineurin and induction of GSK-3β expression may play important roles in the tau hyperphosphorylation seen in tauopathies such as Alzheimer disease (5, 24, 46, 48). Key roles for RCAN1 in human physiology and pathology are rapidly emerging (15). As with many newly discovered genes and proteins, initial confusion over nomenclature often hinders or obscures progress. In this case, the term *DSCR1* for Down syndrome candidate or critical region 1 is misleading, because the gene is not technically inside the DSCR as initially defined. Furthermore, since calcineurin activity is fundamental to so many biological processes, it is likely that RCAN1 and other members of this family of calcineurin regulators will have important functions well beyond those related directly to Down syndrome. Fully aware that these proteins may have additional properties, we propose that the *DSCR1* gene be renamed to reflect its influence on calcineurin signaling.

We have suggested adopting "regulators of calcineurin" for this family of proteins based on the original name given in yeast because it is straightforward and recognizes the concept that calcineurin activity can either increase or decrease depending primarily on the level of RCAN1 induction. The abbreviations *RCAN1, RCAN2,* and *RCAN3* will be used rather than *Rcn1* to avoid confusion with the unrelated *rcn1* gene from Arabidopisis (51) and favoring any existing name. To implement this change, we recommend that publications initially include the *RCAN* and *DSCR* designations as well as the name previously used by the investigator. We hope that all researchers in this exciting and important field will join with us in embracing this new nomenclature. FJ

REFERENCES

1. Fuentes, J. J., Pritchard, M. A., Planas, A. M., Bosch, A., Ferrer, I., and Estivill, X. (1995) A new human gene from the Down syndrome critical region encodes a proline-rich protein highly expressed in fetal brain and heart. *Human Mol. Genet.* **4,** 1935–1944
2. Strippoli, P., Lenzi, L., Petrini, M., Carinci, P., and Zannotti, M. (2000) A new gene family including DSCR1 (Down Syndrome Candidate Region 1) and ZAKI-4: characterization from yeast to human and identification of DSCR1-like 2, a novel human member (DSCR1L2). *Genomics* **64,** 252–263
3. Strippoli, P., Petrini, M., Lenzi, L., Carinci, P., and Zannotti, M. (2000) The murine DSCR1-like (Down syndrome candidate region 1) gene family: conserved synteny with the human orthologous genes. *Gene* **257,** 223–232
4. Crawford, D. R., Leahy, K. P., Abramova, N., Lan, L., Wang, Y., and Davies, K. J. (1997) Hamster adapt78 mRNA is a Down syndrome critical region homologue that is inducible by oxidative stress. *Arch. Biochem. Biophys.* **342,** 6–12
5. Ermak, G., Morgan, T. E., and Davies, K. J. (2001) Chronic overexpression of the calcineurin inhibitory gene DSCR1 (Adapt78) is associated with Alzheimer's disease. *J. Biol. Chem.* **276,** 38787–38794
6. Rothermel, B., Vega, R. B., Yang, J., Wu, H., Bassel-Duby, R., and Williams, R. S. (2000) A protein encoded within the Down syndrome critical region is enriched in striated muscles and inhibits calcineurin signaling. *J. Biol. Chem.* **275,** 8719–8725
7. Fuentes, J. J., Genesca, L., Kingsbury, T. J., Cunningham, K. W., Perez-Riba, M., Estivill, X., and de la Luna, S. (2000) DSCR1, overexpressed in Down syndrome, is an inhibitor of calcineurin-mediated signaling pathways. *Human Mol. Genet.* **9,** 1681–1690
8. Ryeom, S., Greenwald, R. J., Sharpe, A. H., and McKeon, F. (2003) The threshold pattern of calcineurin-dependent gene expression is altered by loss of the endogenous inhibitor calcipressin. *Nat. Immunol.* **4,** 874–881
9. Genesca, L., Aubareda, A., Fuentes, J. J., Estivill, X., De La Luna, S., and Perez-Riba, M. (2003) Phosphorylation of calcipressin 1 increases its ability to inhibit calcineurin and decreases calcipressin half-life. *Biochem. J.* **374,** 567–575
10. Kingsbury, T. J., and Cunningham, K. W. (2000) A conserved family of calcineurin regulators. *Genes Dev.* **14,** 1595–1604
11. Gorlach, J., Fox, D. S., Cutler, N. S., Cox, G. M., Perfect, J. R., and Heitman, J. (2000) Identification and characterization of a highly conserved calcineurin binding protein, CBP1/calcipressin, in *Cryptococcus neoformans*. *EMBO J.* **19,** 3618–3629
12. Lee, J. I., Dhakal, B. K., Lee, J., Bandyopadhyay, J., Jeong, S. Y., Eom, S. H., Kim do, H., and Ahnn, J. (2003) The *Caenorhabditis elegans* homologue of Down syndrome critical region 1, RCN-1, inhibits multiple functions of the phosphatase calcineurin. *J. Mol. Biol.* **328,** 147–156
13. Chang, K. T., Shi, Y. J., and Min, K. T. (2003) The Drosophila homolog of Down's syndrome critical region 1 gene regulates learning: implications for mental retardation. *Proc. Natl. Acad. Sci. U. S. A.* **100,** 15794–15799
14. Ejima, A., Tsuda, M., Takeo, S., Ishii, K., Matsuo, T., and Aigaki, T. (2004) Expression level of sarah, a homolog of DSCR1, is critical for ovulation and female courtship behavior in *Drosophila melanogaster*. *Genetics* **168,** 2077–2087
15. Harris, C. D., Ermak, G., and Davies, K. J. (2005) Multiple roles of the DSCR1 (Adapt78 or RCAN1) gene and its protein

product Calcipressin 1 (or RCAN1) in disease. *Cell Mol. Life Sci.* **62,** 2477–2486
16. Miyazaki, T., Kanou, Y., Murata, Y., Ohmori, S., Niwa, T., Maeda, K., Yamamura, H., and Seo, H. (1996) Molecular cloning of a novel thyroid hormone-responsive gene, ZAKI-4, in human skin fibroblasts. *J. Biol. Chem.* **271,** 14567–14571
17. Yang, J., Rothermel, B., Vega, R. B., Frey, N., McKinsey, T. A., Olson, E. N., Bassel-Duby, R., and Williams, R. S. (2000) Independent signals control expression of the calcineurin inhibitory proteins MCIP1 and MCIP2 in striated muscles. *Circ. Res.* **87,** E61–68
18. Sanna, B., Brandt, E. B., Kaiser, R. A., Pfluger, P., Witt, S. A., Kimball, T. R., van Rooij, E., De Windt, L. J., Rothenberg, M. E., Tschop, M. H., *et al.* (2006) Modulatory calcineurin-interacting proteins 1 and 2 function as calcineurin facilitators in vivo. *Proc. Natl. Acad. Sci. U. S. A.* **103,** 7327–7332
19. Mulero, C., Aubareda, A., Schluter, A., and Perez-Riba, M. (2007) RCAN3, a novel calcineurin inhibitor that down-regulates NFAT-dependent cytokine gene expression. *BBA-Mol. Cell Res.* In press
20. Korenberg, J. R., Chen, X. N., Schipper, R., Sun, Z., Gonsky, R., Gerwehr, S., Carpenter, N., Daumer, C., Dignan, P., Disteche, C., *et al.* (1994) Down syndrome phenotypes: the consequences of chromosomal imbalance. *Proc. Natl. Acad. Sci. U. S. A.* **91,** 4997–5001
21. Sinet, P. M., Theophile, D., Rahmani, Z., Chettouh, Z., Blouin, J. L., Prieur, M., Noel, B., and Delabar, J. M. (1994) Mapping of the Down syndrome phenotype on chromosome 21 at the molecular level. *Biomed. Pharmacother.* **48,** 247–252
22. Casas, C., Martinez, S., Pritchard, M. A., Fuentes, J. J., Nadal, M., Guimera, J., Arbones, M., Florez, J., Soriano, E., Estivill, X., and Alcantara, S. (2001) Dscr1, a novel endogenous inhibitor of calcineurin signaling, is expressed in the primitive ventricle of the heart and during neurogenesis. *Mech. Dev.* **101,** 289–292
23. Fuentes, J. J., Pritchard, M. A., and Estivill, X. (1997) Genomic organization, alternative splicing, and expression patterns of the DSCR1 (Down syndrome candidate region 1) gene. *Genomics* **44,** 358–361
24. Ermak, G., Harris, C. D., Battocchio, D., and Davies, K. J. (2006) RCAN1 (DSCR1 or Adapt78) stimulates expression of GSK-3beta. *FEBS J.* **273,** 2100–2109
25. Hesser, B. A., Liang, X. H., Camenisch, G., Yang, S., Lewin, D. A., Scheller, R., Ferrara, N., and Gerber, H. P. (2004) Down syndrome critical region protein 1 (DSCR1), a novel VEGF target gene that regulates expression of inflammatory markers on activated endothelial cells. *Blood* **104,** 149–158
26. Minami, T., Horiuchi, K., Miura, M., Abid, M. R., Takabe, W., Noguchi, N., Kohro, T., Ge, X., Aburatani, H., Hamakubo, T., *et al.* (2004) Vascular endothelial growth factor- and thrombin-induced termination factor, Down syndrome critical region-1, attenuates endothelial cell proliferation and angiogenesis. *J. Biol. Chem.* **279,** 50537–50554
27. Cano, E., Canellada, A., Minami, T., Iglesias, T., and Redondo, J. M. (2005) Depolarization of neural cells induces transcription of the Down syndrome critical region 1 isoform 4 via a calcineurin/nuclear factor of activated T cells-dependent pathway. *J. Biol. Chem.* **280,** 29435–29443
28. U, M., Shen, L., Oshida, T., Miyauchi, J., Yamada, M., and Miyashita, T. (2004) Identification of novel direct transcriptional targets of glucocorticoid receptor. *Leukemia* **18,** 1850–1856
29. Mammucari, C., Tommasi di Vignano, A., Sharov, A. A., Neilson, J., Havrda, M. C., Roop, D. R., Botchkarev, V. A., Crabtree, G. R., and Dotto, G. P. (2005) Integration of Notch 1 and calcineurin/NFAT signaling pathways in keratinocyte growth and differentiation control. *Dev. Cell* **8,** 665–676
30. Leahy, K. P., and Crawford, D. R. (2000) adapt78 protects cells against stress damage and suppresses cell growth. *Arch. Biochem. Biophys.* **379,** 221–228
31. Ermak, G., Harris, C. D., and Davies, K. J. (2002) The DSCR1 (Adapt78) isoform 1 protein calcipressin 1 inhibits calcineurin and protects against acute calcium-mediated stress damage, including transient oxidative stress. *FASEB J.* **16,** 814–824
32. Rothermel, B. A., Vega, R. B., and Williams, R. S. (2003) The role of modulatory calcineurin-interacting proteins in calcineurin signaling. *Trends Cardiovasc. Med.* **13,** 15–21
33. Cao, X., Kambe, F., Miyazaki, T., Sarkar, D., Ohmori, S., and Seo, H. (2002) Novel human ZAKI-4 isoforms: hormonal and tissue-specific regulation and function as calcineurin inhibitors. *Biochem. J.* **367,** 459–466
34. Cao, X., Kambe, F., Moeller, L. C., Refetoff, S., and Seo, H. (2005) Thyroid hormone induces rapid activation of Akt/protein kinase B-mammalian target of rapamycin-p70S6K cascade through phosphatidylinositol 3-kinase in human fibroblasts. *Mol. Endocrinol.* **19,** 102–112
35. Canaider, S., Facchin, F., Griffoni, C., Casadei, R., Vitale, L., Lenzi, L., Frabetti, F., D'Addabbo, P., Carinci, P., Zannotti, M., and Strippoli, P. (2006) Proteins encoded by human Down syndrome critical region gene 1-like 2 (DSCR1L2) mRNA and by a novel DSCR1L2 mRNA isoform interact with cardiac troponin I (TNNI3). *Gene* **372,** 128–136
36. Vega, R. B., Rothermel, B. A., Weinheimer, C. J., Kovacs, A., Naseem, R. H., Bassel-Duby, R., Williams, R. S., and Olson, E. N. (2003) Dual roles of modulatory calcineurin-interacting protein 1 in cardiac hypertrophy. *Proc. Natl. Acad. Sci. U. S. A.* **100,** 669–674
37. Hilioti, Z., Gallagher, D. A., Low-Nam, S. T., Ramaswamy, P., Gajer, P., Kingsbury, T. J., Birchwood, C. J., Levchenko, A., and Cunningham, K. W. (2004) GSK-3 kinases enhance calcineurin signaling by phosphorylation of RCNs. *Genes Dev.* **18,** 35–47
38. Lin, H. Y., Michtalik, H. J., Zhang, S., Andersen, T. T., Van Riper, D. A., Davies, K. K., Ermak, G., Petti, L. M., Nachod, S., Narayan, A. V., *et al.* (2003) Oxidative and calcium stress regulate DSCR1 (Adapt78/MCIP1) protein. *Free Radic. Biol. Med.* **35,** 528–539
39. Chan, B., Greenan, G., McKeon, F., and Ellenberger, T. (2005) Identification of a peptide fragment of DSCR1 that competitively inhibits calcineurin activity in vitro and in vivo. *Proc. Natl. Acad. Sci. U. S. A.* **102,** 13075–13080
40. Hogan, P. G., Chen, L., Nardone, J., and Rao, A. (2003) Transcriptional regulation by calcium, calcineurin, and NFAT. *Genes Dev.* **17,** 2205–2232
41. Aubareda, A., Mulero, M. C., and Perez-Riba, M. (2006) Functional characterization of the calcipressin 1 motif that suppresses calcineurin-mediated NFAT-dependent cytokine gene expression in human T cells. *Cell Signal* **18,** 1430–1438
42. Vega, R. B., Yang, J., Rothermel, B. A., Bassel-Duby, R., and Williams, R. S. (2002) Multiple domains of MCIP1 contribute to inhibition of calcineurin activity. *J. Biol. Chem.* **277,** 30401–30407
43. Fox, D. S., and Heitman, J. (2005) Calcineurin-binding protein Cbp1 directs the specificity of calcineurin-dependent hyphal elongation during mating in *Cryptococcus neoformans*. *Eukaryot. Cell* **4,** 1526–1538
44. Abbasi, S., Lee, J. D., Su, B., Chen, X., Alcon, J. L., Yang, J., Kellems, R. E., and Xia, Y. (2006) Protein kinase-mediated regulation of calcineurin through the phosphorylation of modulatory calcineurin-interacting protein 1. *J. Biol. Chem.* **281,** 7717–7726
45. Rothermel, B. A., McKinsey, T. A., Vega, R. B., Nicol, R. L., Mammen, P., Yang, J., Antos, C. L., Shelton, J. M., Bassel-Duby, R., Olson, E. N., and Williams, R. S. (2001) Myocyte-enriched calcineurin-interacting protein, MCIP1, inhibits cardiac hypertrophy in vivo. *Proc. Natl. Acad. Sci. U. S. A.* **98,** 3328–3333
46. Ermak, G., and Davies, K. J. (2003) DSCR1(Adapt78)—a Janus gene providing stress protection but causing Alzheimer's disease? *IUBMB Life* **55,** 29–31
47. Ermak, G., Cheadle, C., Becker, K. G., Harris, C. D., and Davies, K. J. (2004) DSCR1(Adapt78) modulates expression of SOD1. *FASEB J.* **18,** 62–69
48. Harris, C. D., Ermak, G., and Davies, K. J. A. (2007) RCAN1–1L is overexpressed in neurons of Alzheimer patients. *FEBS J.* In press
49. Cook, C. N., Hejna, M. J., Magnuson, D. J., and Lee, J. M. (2005) Expression of calcipressin1, an inhibitor of the phosphatase calcineurin, is altered with aging and Alzheimer's disease. *J. Alzheimers Dis.* **8,** 63–73
50. Arron, J. R., Winslow, M. M., Polleri, A., Chang, C. P., Wu, H., Gao, X., Neilson, J. R., Chen, L., Heit, J. J., Kim, S. K., *et al.* (2006) NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. *Nature* **441,** 595–600
51. Garbers, C., DeLong, A., Deruere, J., Bernasconi, P., and Soll, D. (1996) A mutation in protein phosphatase 2A regulatory subunit A affects auxin transport in Arabidopsis. *EMBO J.* **15,** 2115–2124

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