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**Commentary**

Familial neurohypophyseal diabetes insipidus (FNDI) in humans is an autosomal dominant disorder caused by a variety of mutations in the arginine vasopressin (AVP) precursor. A new report demonstrates how heterozygosity for an AVP mutation causes FNDI (see the related article beginning on page 1697). Using an AVP knock-in mutation in mice, the study shows that FNDI is caused by retention of AVP precursors and progressive loss of AVP-producing neurons.



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# Dominant-negative diabetes insipidus and other endocrinopathies

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**Familial neurohypophyseal diabetes insipidus (FNDI) in humans is an autosomal dominant disorder caused by a variety of mutations in the arginine vasopressin (AVP) precursor. A new report demonstrates how heterozygosity for an AVP mutation causes FNDI (see the related article beginning on page 1697). Using an AVP knock-in mutation in mice, the study shows that FNDI is caused by retention of AVP precursors and progressive loss of AVP-producing neurons.**

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## Autosomal recessive, autosomal dominant, and dominant-negative mutations

Genes are transcribed into mRNA, which is translated into a protein product. In the case of arginine vasopressin (AVP), the protein product is synthesized as a much larger prohormone, which includes AVP, its carrier protein called neurophysin, and a glycoprotein.

The activity of different versions of genes (called alleles) and the quantitative and qualitative characteristics of their respective gene products can be correlated with the incidence and severity of disease. For example, the sums of the amounts of gene products synthesized from both alleles at an autosomal locus, representing the net activity of gene expression, are shown in Figure 1. When one of two paired alleles produces sufficient protein to overcome the presence of a mutation in the second allele, homeostasis is maintained and clinical manifestations of protein deficiency do not occur. In such cases, the related disorder is characterized by an autosomal recessive (AR) mode of inheritance, and the heterozygous carrier does not manifest clinical symptoms of disease (Figure 1a, left). However, when the net activity of gene expression of two mutant alleles is not sufficient to prevent disease, such as in the case of Brattleboro rats homozygous for a single-base deletion in exon 2 of both AVP genes, diabetes insipidus with an AR mode of inheritance occurs (ref. 1; Figure 1a, right).

In contrast, when a single normal allele does not have sufficient gene-expression activity to prevent clinical symptoms of disease, the heterozygous individual is affected and the disorder is characterized by an autosomal dominant (AD) mode of inheritance (Figure 1b). For example, familial neurohypophyseal diabetes insipidus (FNDI) occurs in subjects heterozygous for a variety of *AVP* gene mutations.

When a mutation in one allele prevents both it and the normal allele from producing sufficient gene product to prevent clinical symptoms, the disorder is also characterized by an AD mode of inheritance (Figure 1c). Note that the sum of the gene-expression activities of the mutant and normal alleles is less than that of a single normal allele, because of the effect of the dominant-negative (DN) mutation on the normal allele (Figure 1c). The DN mutation decreases expression of the normal gene in the same cell so that the sum of their gene expression does not reach the threshold needed to prevent disease.

## FNDI

Both the AVP and the oxytocin (OT) prohormones are synthesized in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus (2). AVP and OT are produced by separate populations of magnocellular neurons in both nuclei, packaged into neurosecretory vesicles with the neurophysins, and transported to the neurohypophysis, where they are either stored or secreted into the circulation.

In three members in three generations of a Japanese family with FNDI, Nagasaki et al. (3) found a TGC-to-TGA transversion at nucleotide position 1891 that encodes a Cys67Ter change. The prematurely terminated AVP product was predicted to lack part of the neurophysin II and glycoprotein moieties. While the function of AVP is well characterized, and neurophysin II is known to act as a carrier protein, the function of the glycopro-

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**Nonstandard abbreviations used:** arginine vasopressin (AVP); autosomal recessive (AR); autosomal dominant (AD); familial neurohypophyseal diabetes insipidus (FNDI); dominant-negative (DN); oxytocin (OT); supraoptic nucleus (SON); paraventricular nucleus (PVN); growth hormone (GH); isolated GH deficiency type II (IGHD II).

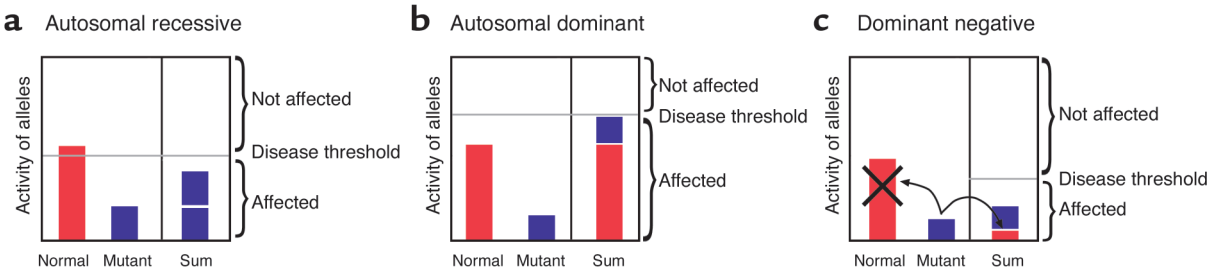


**Figure 1**
Relationships of levels of gene expression, reflected as the activity of single homologous alleles (left) and the sum of the activities of the two homologous alleles (right). The dashed line represents the minimal sum of allelic activity required to prevent autosomal recessive (**a**), autosomal dominant (**b**), and dominant-negative (**c**) disorders.

tein moiety is not well understood (see Online Mendelian Inheritance in Man [OMIM] entry no. 125700, ref. 4). To determine how AVP mutations cause FNDI, Nijenhuis et al. (5) stably expressed mutant AVP prohormones in neuroendocrine cell lines. Processing and secretion of all mutant hormones were impaired, resulting in accumulation of high concentrations of mutant prohormone in the ER. The authors concluded that mutant AVP prohormones accumulated in and caused degeneration of the neurons in which they were expressed and accounted for the AD mode of inheritance associated with FNDI.

In this issue of the *JCI*, Russell et al. (6) report additional studies that elucidate the mechanism by which heterozygosity for the Cys67Ter substitution or the substitution of threonine for alanine at the –1 position [A(–1)T] in AVP causes FNDI. The authors created murine models of FNDI using knock-ins of both mutations. In a knock-in, only one normal murine and one DN allele (either Cys67Ter or A(–1)T) are present, and the effects of the DN allele can be examined in vivo (Figures 1c and 2). By analysis of water intake, urine output and osmolarity, and serum AVP levels, the authors found that the Cys67Ter heterozygous mice developed progressive FNDI and that the ratio of AVP to oxytocin (OT) neurons in the PVN and SON decreased progressively with age. The A(–1)T knock-in did not cause FNDI, presumably because its aberrant prepro-hormone AVP product that retains the signal peptide is less toxic. Russell et al. conclude that the mutant Cys67Ter and normal AVP products form complexes that impair secretion,

**Table 1**
Examples of dominant-negative mutations that cause endocriopathies

| OMIM number | Gene, protein | Genetic disorder |
|---|---|---|
| 139250[A] | *GH1*, growth hormone 1 | Growth hormone deficiency |
| 173110[A] | *POU1F1*, POU domain, class 1, transcription factor 1 | Combined pituitary hormone deficiency |
| 173100[B] | *GH1*, growth hormone 1 | Isolated growth hormone deficiency, type II; pituitary dwarfism |
| 262500[B] | *GHR*, growth hormone receptor | Laron dwarfism, type I |
| 138040[A] | *GCCR*, glucocorticoid receptor | Familial glucocorticoid resistance |
| 600946[A] | *GHR*, growth hormone receptor | Laron dwarfism, type I |
| 301500[A] | *GLA*, α-galactosidase A | Fabry disease |
| 300200[A] | *DAX1*, dosage-sensitive sex reversal–adrenal hypoplasia gene on the X chromosome, gene 1 | Congenital adrenal hypoplasia |
| 190160[A] | *THRB*, thyroid hormone receptor β | Thyroid hormone resistance |
| 193400[A] | *VWF*, von Willebrand factor | von Willebrand disease |
| 191740[A] | *UGT1A1*, uridine diphosphate glycosyltransferase 1 | Gilbert syndrome, Crigler-Najjar syndrome |
| 194070[B] | *WT1*, Wilms tumor-1 gene | Denys-Drash syndrome |
| 147370[A] | *IGF1R*, insulin-like growth factor 1 receptor | Diabetes in mice |
| 601487[A] | *PPARG*, peroxisome proliferator–activated receptor γ | Severe insulin resistance, diabetes mellitus, and hypertension |
| 160900[B] | *DMPK*, dystrophia myotonica protein kinase | Myotonic dystrophy |
| 155541[A] | *MC4R*, melanocortin-4 receptor | Obesity |
| 180245[A] | *RXRA*, retinoic acid receptor α | Acute promyelocytic leukemia |
| 145980[B] | *CASR*, calcium-sensing receptor | Familial hypocalciuric hypercalcemia |
| 600140[A] | *CREBBP*, CREB-binding protein | Rubinstein-Taybi syndrome |
| 601199[A] | *CASR*, calcium-sensing receptor | Familial hypocalciuric hypercalcemia |
| 600733[A] | *IPF1*, insulin promoter factor 1 | Pancreatic agenesis |

A search for the keyword phrase "dominant-negative hormone deficiency" in the OMIM database (4), a catalog of human genes and genetic disorders, revealed 33 entries, of which 21 were selected (see text). [A]The phenotype determined by the gene at the given locus is separate from those represented by other entries marked with footnote letter A, and the mode of inheritance of the phenotype has been proved. [B]These entries are descriptive, usually of a phenotype, and do not represent a unique locus.

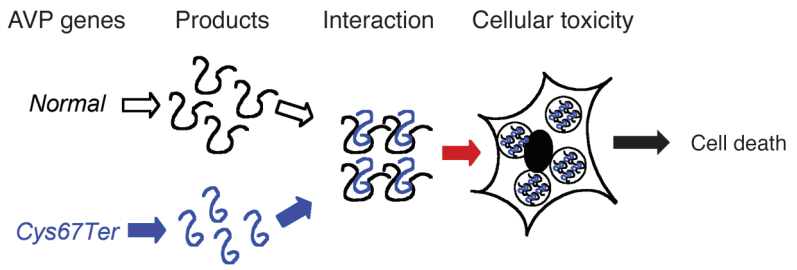


**Figure 2**
In the pathogenesis of FNDI, normal and Cys67Ter AVP products interact to prevent AVP secretion. These products also accumulate within, damage, and cause loss of AVP secretory cells.

and that accumulation of these complexes in the ER causes cellular toxicity and progressive loss of AVP-producing neurons (Figure 2). This contrasts with the understanding that DN mutations of genes encoding polymeric molecules, such as collagen, usually adversely affect the normal gene product within the same cell by dimerizing or combining with the normal product in a way that inactivates it. Furthermore, in the cases of polymeric molecules, DN mutations are often more deleterious than mutations that cause no gene product to be produced, which are referred to as null mutations or null alleles. Since AVP is a monomeric protein, it is unclear why and how these complexes form, and the mechanism by which the Cys67Ter mutation acts as a DN must be different. Possibly, the A(–1)T mutation functions in mice more like a null allele than does the Cys67Ter mutation and thus does not cause murine FNDI. In any case, the findings of Russell et al. may also explain some of the clinical variability observed in FNDI patients.

## Are other endocrine disorders caused by DN mutations?

To determine whether the findings of Russell et al. (6) may apply to other endocrine disorders, I did an OMIM search using the keyword phrase "dominant-negative hormone deficiency." I found that 21 of 33 matching OMIM entries included data on true DN mutations related to endocrine disorders (Table 1), indicating that DN mutations cause a variety of endocrine diseases. For example, the first entry is growth hormone (GH). In isolated GH deficiency type II (IGHD II), multiple different DN GH mutations cause increased expression of a 17.5-kDa isoform of GH (7). Overproduction of this isoform in transgenic mice prevented maturation of GH secretory vesicles and caused accumulation of a large GH aggregate. This accumulation led to the death of the majority of the somatotrophs, and the few remaining somatotrophs were morphologically abnormal (8, 9). Thus the DN GH mutation leads to loss of the majority of somatotrophs, causing anterior pituitary hypoplasia and IGHD II, analogous to the studies presented in this issue by Russell et al. (6).

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