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Genetic forms of neurohypophyseal diabetes insipidus

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Abstract

In the majority of cases, hereditary neurohypophyseal diabetes insipidus (DI) is a monogenic disorder caused by mutations in the *AVP* gene. Dominant transmission is by far the most common form. In these patients, symptoms develop gradually at various ages during childhood, progressing with complete penetrance to polyuria and polydipsia that is usually severe. In autosomal dominant neurohypophyseal DI (ADNDI), the mutant prohormone is folding deficient and consequently retained in the ER, where it forms amyloid-like fibrillar aggregates. Degradation by proteasomes occurs, but their clearance capacity appears to be insufficient. Postmortem studies in affected individuals suggest a neurodegenerative process confined to vasopressinergic neurons. Other forms of genetic neurohypophyseal DI include the very rare autosomal recessive type, also caused by mutations in the *AVP* gene, and complex multiorgan disorders, such as Wolfram syndrome. In all individuals where a congenital form of DI is suspected, including nephrogenic types, genetic analysis should be performed.

Key Words

Diabetes insipidus, neurogenic; neurohypophyseal, vasopressin; neurophysin; hereditary; copeptin

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1. Introduction

Polyuria, i.e. the production of >45-50 ml of hypotonic (<300 mOsmol/kg) urine per kg body weight and day under ad libitum fluid intake, is the hallmark of untreated diabetes insipidus (1, 2) (DI; Greek and Latin for “tasteless water flow”). If the thirst mechanism is intact, patients deprived of free access to fluids experience excessive thirst (polydipsia). DI results from disturbances in the antidiuretic system either at the hypothalamic/hypophyseal level (central or neurohypophyseal DI), or – in the case of nephrogenic DI - from insufficient response of the renal type 2 receptor (AVPR2) to the antidiuretic hormone arginine vasopressin (AVP). “Primary polydipsia” refers to a form of DI that results from physiologically suppressed AVP secretion due to excessive fluid intake, either because of alterations in the thirst mechanism (“dipsogenic DI”) or a psychologically motivated habit (“psychogenic DI”). In primary polydipsia as well as pituitary or nephrogenic DI with large fluid throughput, the renal urinary concentration capacity may be reduced due to partial washout of the corticomedullary osmogradient, potentially complicating the differential diagnosis based on measurements of urinary osmolality alone (3). Pregnancy-associated DI is caused by increased activity of a placental vasopressinase, leading to inadequately low circulating AVP concentrations. Vasopressinase-mediated, acute DI has also been observed after placental abruption (4).

Table 1 gives an overview over the differential diagnosis of DI. Both central and nephrogenic DI may have a genetic basis. This review will discuss the pathophysiology of the various forms of hereditary neurohypophyseal DI, focusing on clinical characteristics, the impact of mutations in the *AVP* gene on vasopressinergic neurons, and the role of the cellular quality control system with respect to water homeostasis.

2. Historical aspects and early histopathological findings

In 1841, the French physician L.-U. Lacombe was the first to describe hereditary DI in an extensive report on 29 clinical "*observations*" (5). Large DI family trees were subsequently published by German authors in the late 19th and early 20th century (6-8). During the Nazi period, a German textbook shockingly commented with respect to hereditary DI that *"…..The reproduction of this variety of diabetics is equally undesirable. For as harmless as this constitutional anomaly may be under ordinary circumstances, as dangerous it might become for those participating in a war, for example."* (translated from German by J.R. from (9)). Histopathological alterations in deceased patients with hereditary or "idiopathic" neurohypophyseal DI were acknowledged at about the same time (10) and later confirmed in several publications (11-15). The authors described paucity of magnocellular AVP-producing neurons and mild gliosis in the hypothalamic parvocellular and supraoptic nuclei, as evidenced by brain sections prepared post mortem. These findings suggested a degenerative process confined specifically to vasopressinergic neurons, constituting the basis for the "neurotoxicity hypothesis".

The genes encoding the human vasopressin and oxytocin preprohormones were cloned in 1985 (16), paving the way for the identification of the first mutation in the *AVP* gene (17) and its expression in cell culture experiments and transgenic animal models (18).

3. Clinical presentation and differential diagnosis of hereditary diabetes insipidus

Table 2 gives an overview over the different forms of DI with a genetic background. If DI is a component of a rare multiorgan disease, such as Wolfram syndrome, signs and symptoms other than polyuria/polydipsia may prevail (see paragraphs 5.2 and 5.3 on syndromic DI below). However, in the majority of cases, the disorder is caused by mutations in the *AVP* gene. In the case of the very rare autosomal recessive form, polyuria may manifest acutely in the neonatal period (19, 20), putting

the child in danger of severe, even life-threatening dehydration. This clinical feature may equally be observed in hereditary nephrogenic DI due to mutations in the *AVPR2-* or *Aquaporin 2* - genes (21). In sharp contrast, symptoms in autosomal-dominant neurohypophyseal DI (ADNDI) manifest later in childhood and develop gradually to polyuria that is usually severe (3, 18, 22). There is no clear genotype-phenotype correlation in ADNDI, with the exception that certain mutations resulting in partial signal cleavage in prepro-AVP-neurophysin II (NPII) tend to cause milder symptoms and later onset (2, 23-25) than mutations occurring in the NPII moiety or those abolishing signal cleavage completely (26, 27). The reason for this observation is most likely residual antidiuretic hormone secretion of fully cleaved, biologically active hormone until the vasopressinergic neurons have eventually been eliminated. Interestingly, the clinical presentation may vary considerably between families and even family members carrying the same mutation in the *AVP* gene (23, 28, 29). Another unexplained observation is that polyuria may regress with increasing age (29-31).

As in other forms of diabetes insipidus, children affected with ADNDI who are not properly treated or refused appropriate access to fluids develop failure to thrive, which may be reversed upon treatment with synthetic AVP (DDAVP) (19, 32-34). Another potential consequence of untreated chronic polyuria, be it due to neurogenic (35) or nephrogenic (36-38) DI, is dilation of the ureters and bladder (21), which predisposes to vesicoureteral reflux and ascending urinary tract infections, as well as secondary renal failure. The prevalence of these complications is unknown, but they may be more frequent in persistent nephrogenic DI, such as the inherited types, since treatment is less efficient than neurohypophyseal DI.

Diagnosis in all hereditary forms of DI should be established by medical history, clinical and laboratory testing and – if possible - genetic analysis. If a hereditary background is known or suspected, genetic analysis is always advised and may make strenuous clinical testing superfluous, particularly in children. Importantly, a

negative family history does not rule out a genetic cause of DI, as mutations may occur *de novo* (39, 40), or a previously asymptomatic recessive form may be present (41).

Polyuria must be differentiated from pollakisuria and should be quantified; if present, other causes such as uncontrolled diabetes mellitus, hypercalcaemia, or hypokalaemia must be excluded. Measurement of copeptin, the C-terminal glycopeptide of the AVP prohormone (Figure. 1), has proven very helpful to differentiate nephrogenic DI, neurohypophyseal DI, and primary polydipsia (42, 43). Copeptin is stoichiometrically cosecreted with AVP from the posterior pituitary and can thus serve as surrogate marker for vasopressin (44). Since copeptin, unlike vasopressin, is stable and reliably measured in serum or plasma, commercially available assays (e.g. ref. (45)) help circumvent the technically demanding AVP radioimmunoassays, which never entered clinical routine, or the commercially available AVP assays of questionable validity. In an adult patient presenting with a suggestive history and confirmed polyuria/polydipsia, an elevated unstimulated circulating copeptin level >21.4 pM establishes the diagnosis of nephrogenic DI (42, 43). If the copeptin concentration is lower, it is adequate in most cases to perform a stimulatory test , e.g. by water deprivation, hypertonic saline infusion (43) or arginine infusion (46).

4. Monogenic neurohypophyseal diabetes insipidus: mutations in the *AVP* gene.

The *AVP* gene, located on chromosome 20p13 and separated from the homologous *Oxytocin* gene by a ~12 kilobase sequence, has three exons separated by two introns. The gene encodes prepro-vasopressin-neurophysin II, consisting of the 21-amino acid (aa) N-terminal signal peptide (SP), the nonapeptide AVP, the “carrier” protein neurophysin II (NPII) of 93 aa, and the C-terminal 39-aa glycopeptide, termed copeptin (Figure 1) (47). The latter is lacking in prepro-oxytocin-neurophysin I, which

facilitated the development of an assay for highly specific detection and quantification of the antidiuretic capacity in the differential diagnosis of polyuric syndromes. Figure 2 depicts the regulated secretion of vasopressin from magnocellular neurons in the supraoptic and paraventricular hypothalamic nuclei. During synthesis at the ribosome, the nascent polypeptide chain is translocated into the lumen of the endoplasmic reticulum (ER). During translocation, the SP is cotranslationally cleaved. Subsequently, the prohormone AVP-NPII-copeptin folds in the ER lumen, which involves the binding of AVP into a binding pocket in NPII (48, 49), and is transported through the Golgi apparatus to the trans-Golgi network, where it is sorted into neurosecretory granules and cleaved into AVP, NPII and copeptin. Granules are axonally transported from the cell bodies to cell endings in the posterior pituitary. AVP, NPII and copeptin are cosecreted into the circulation by regulated secretion upon various stimuli, most notably hyperosmolality and hypovolaemia. While copeptin has been found to mediate granule sorting and regulated secretion (50), there is no known function for both copeptin and NPII after secretion into the circulation.

Since the first publication in 1991 (17), numerous mutations causing hereditary neurogenic diabetes insipidus have been reported. Currently, the public and professional domains of the Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk) list 75 and 87 variants, respectively, most of them being missense/nonsense mutations. Deletions, indels and splice mutations account for a minority of reported cases. All mutations reported so far have occurred in the gene regions encoding the signal peptide, AVP, or neurophysin II (Figure 1). The disease is usually transmitted in a dominant fashion, but rarely, families with recessive phenotypes have been reported. Interestingly, in one Chinese family with autosomal dominant transmission of neurohypophyseal DI, no mutation could be identified in the *AVP* gene or its promoter, although linkage to a 7-centiMorgan interval on chromosome 20p13 was shown (51).

4.1. Autosomal dominant neurohypophyseal DI

This is by far the most common form, accounting for >90% of reported family trees. Its pathogenesis is discussed in detail in section 6 below.

4.2. Autosomal recessive neurohypophyseal DI

Four family trees with a recessive mode of inheritance have been reported so far. Affected members of two seemingly unrelated consanguineous Palestinian families from Texas (32) and Israel (19) were homozygous for a point mutation in the gene domain encoding AVP, replacing proline at position 7 by leucin (P7L). The mutant protein is correctly trafficked through and secreted from the cell (52), but its binding affinity to the renal receptor is decreased ~30-fold (32). In another consanguineous English family originating from Pakistan, hypernatraemia, serum hyperosmolality and low concurrent urine osmolality occurred in the index patient during the first few days of life (20). His physicians documented failure to thrive. The father of the proband and several relatives also had DI, with the onset of symptoms reported between 3 and 11 months. Genetic analysis revealed a large deletion of ~10 kilobases on both alleles in the index patient and other affected family members, encompassing most of the *AVP* gene, its regulatory sequences and the intergenic region between the *AVP* and oxytocin (*OTX*) genes. This deletion likely abolishes transcription of the *AVP* gene. In a Canadian family without any history of DI, the index patient was born to asymptomatic parents, presenting with polyuria, polydipsia and failure to thrive in the first months of life (41). Analysis of the *AVP* gene showed compound heterozygosity of the P7L mutation and a novel point mutation at the splice-acceptor site of intron 1.

In contrast to early-onset signs and symptoms in nephrogenic DI, affected individuals of all four families with recessive neurogenic DI were responsive to

treatment with DDAVP. As noted above, the report by Bourdet et al. highlights the importance of genetic testing even in the absence of a family history.

5. X-linked and syndromic forms of genetic neurohypophyseal DI

5.1. X-linked: the unidentified gene

To date, one preliminary report on a family with X-linked transmission has been published (53). Males develop DDAVP-sensitive DI as infants or during early childhood, and the extent of AVP deficiency varies (3). The responsible gene links to chromosome Xq28 but has not been identified. Importantly, both the *AVP* and *AVPR2* genes harbor no mutations.

5.2 Wolfram syndrome

DDAVP-responsive partial or severe DI (54) is a component of the Wolfram syndrome 1, or DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, sensorineural Deafness) (55). This rare, progressive neurodegenerative disorder is transmitted in an autosomal recessive fashion, with homozygous or compound heterozygous mutations occurring in the responsible Wolframin (*WFS1*) gene located on chromosome 4p16.1 (56, 57). Diagnostic criteria typically include only juvenile onset diabetes mellitus and progressive optic atrophy, but the diagnosis may be missed if the age criterion is used stringently (58), because symptoms may manifest after the age of 18 years. DI has been reported to be present in 29% (59) to 73% (60) of affected patients, occurring at a median age of ~15 years. Other clinical characteristics include renal tract abnormalities, psychiatric symptoms such as depression with a high suicide risk (61, 62), and neurological complications resulting from brain stem and cerebellar pathology, such as gait ataxia, horizontal nystagmus, dysarthria, or central apnoea. Manifestation of urinary tract and neurological disease may peak at age 20 and 30 years, respectively, depending on the genotype (58).

Death occurs at a median age of 30 years (60) as a consequence of respiratory complications.

WFS1 encodes a calcium channel with 9 transmembrane domains across the ER membrane (57). The mutations are distributed throughout the gene without detectable hot spots, and may lead to degradation of aberrant mRNA or of unfolded wolframin (58). Wolframin deficiency causes ER stress and triggers apoptosis in neuronal and pancreatic beta cells (63).

5.3. Neurohypophyseal DI in the context of malabsorptive diarrhoea

Mutations in the proprotein convertase subtilisin/kexin type 1 (*PCSK1*) gene have been identified in children with severe obesity, malabsorptive diarrhoea and various endocrine disorders (64, 65). This rare, complex gastrointestinal and endocrine syndrome is transmitted in an autosomal-recessive fashion. The *PCSK1* gene is expressed mainly in the brain, adrenal gland and gastrointestinal tract, including the pancreas (https://www.ncbi.nlm.nih.gov/gene/5122#gene-expression). It encodes proprotein convertase 1/3 (PC1/3), a serine protease that processes prohormones synthesized in neuroendocrine and enteroendocrine cells, e.g. proinsulin or proopiomelanocortin (POMC), into mature peptides (66). Accordingly, endocrine and metabolic consequences of PC1/3 deficiency include hyperphagia (67), hypocortisolism, hypogonadotropic hypogonadism, impaired glucose tolerance (68), growth hormone deficiency, central hypothyroidism, and DDAVP-sensitive DI (65, 69, 70). DI typically manifests before the age of 5 years (70), with the average age of onset being approximately 18 months of age (65). These pathologies apparently are of hypothalamic/pituitary origin.

6. Pathogenesis of autosomal-dominant neurohypophyseal diabetes insipidus (ADNDI)

Many *AVP* gene mutations associated with ADNDI have been studied in heterologous expression experiments using various cell lines, and a small number has been expressed in transgenic animals.

6.1. ER retention and ER-associated degradation of folding-incompetent mutant AVP precursor hormones

The ER represents the quality-control site in eukaryotic cells, permitting exit to the Golgi apparatus only to correctly folded proteins (71) (Figure 2). ER-resident chaperones, such as binding protein (BiP), calreticulin, or protein disulfide isomerase (PDI) associate with nascent polypeptides, facilitating the assumption of the correct three-dimensional conformation and preventing their aggregation. Prolonged association of misfolded proteins with chaperones, which are themselves resident in the ER due to an ER retention motif in their primary structure, results in ER retention and eventually retrotranslocation into the cytoplasm (72), where the mutant protein is hydrolyzed by the proteasome (see Figure 4 for more details). ER retention and ER-associated degradation (ERAD) has been demonstrated for multiple dominant pro-AVP variants, e.g. the ΔG227 mutant, which abolishes cleavage of the signal peptide from the prohormone chain (27) (Figure 3), and other mutations occurring in the signal peptide or NPII moieties (73). Notably, a significant portion of wild type provasopressin is also substrate for proteasomal degradation, because retrotranslocation occurs apparently due to relatively inefficient folding, and because the preprohormone is synthesised in part into the cytosol due to relative targeting inefficiency of the signal sequence in (73).

The fact that in ADNDI only one allele carries a pathogenic mutation implicates a dominant-negative effect on the wild type counterpart, which eventually leads to the typical symptoms and histological findings described in paragraphs 2 and 3. Several mechanisms have been specifically implied in the pathogenesis of ADNDI. Since AVP prohormone molecules form homodimers (74), the mutant may hinder secretion

of wild type molecules. There is experimental evidence for such interaction (75); however, this mechanism explains neither the progressive nature of the disease nor the available histopathological data and can thus not be solely responsible for them.

If the amount of proteins populating the ER exceeds its folding capacity, a number of pathways, collectively called the ER stress response or unfolded protein response (UPR), are activated (76-78), leading to increased expression of ER chaperones while generally repressing protein synthesis. In some instances, apoptotic pathways may become activated (79, 80). Stable expression of an ADNDI truncation mutant in a mouse neuroblastoma cell line (81) and in a transgenic knock-in mouse model (82) has been reported to cause cell death as evidenced by immunostaining; but it has been questioned by other researchers whether cytotoxicity is primarily responsible for the phenotype, as transgenic mice expressing the same truncation mutant have reproduced the phenotype even prior to neuronal loss, suggesting a functional defect preceding the neurotoxic effect of the pro-AVP mutant (83). Notably, apoptosis markers were detectable neither in the cell culture nor the mouse experiments. Rather, electron microscopic examination of vasopressinergic neurons in the DI mice revealed dilated ER cisternae containing large aggregations, as well as cell loss associated with autophagy, a lysosomal degradation mechanism (84). Whether autophagy should be viewed as epiphenomenon, a potentially reparative process, or - conversely - causative for neuronal cell death currently remains unclear.

6.2 ER-associated fibrillar aggregation of mutant AVP prohormone

It was observed in early immunofluorescence studies that dominant pro-AVP mutants form aggregates located in the ER (81). Our group has studied this process in detail. When expressed in COS fibroblast cells, mutant pro-AVP clusters in large structures, consisting of disulfide-linked provasopressin polymers (27). The aggregations accumulate progressively after transfection of cultured cells and are composed of amyloid-like fibrils formed by the AVP precursor (52). In this respect, and considering

the apparent cell loss of vasopressinergic neurons in animal and *post mortem* human studies, ADNDI bears resemblance to neurodegenerative disorders characterized by amyloid aggregates. However, while in Parkinson's, Alzheimer's or Huntington's disease aggregations are cytosolic or extracellular, pro-AVP aggregation occurs in the ER.

ER chaperones co-localize with pro-AVP in the aggregates, as evidenced by immunohistochemistry and immunogold electron microscopy (Figure 5). Aggregates from pathogenic pro-AVP mutants are observed not only in transfected fibroblast and mouse neuronal cell lines, but also *in vitro* for the purified protein under oxidative conditions (52). Aggregate formation in the ER is abolished when the 16 cysteine residues of the prohormone (Figure 1) are replaced by serine, indicating that disulfide links are necessary to stabilize aggregates in the ER (52).

We explored the relation between pathological aggregate formation of ADNDI mutants and the physiological self-aggregation occurring in the trans-Golgi network. This process is essential in the formation of secretory granules containing regulated cargo proteins and has been proposed to represent the formation of "functional amyloids" (85). To identify the provasopressin sequences containing the potential for aggregate formation, a number of artificial scanning and deletion mutants were expressed in neuronal cell lines. Analysis by biochemical methods, immunohistochemistry and immunogold electron microscopy demonstrated that the same two prohormone domains, namely AVP at the N-terminus and the C-terminal copeptin, independently confer ER aggregation as well as granule sorting and regulated secretion of the precursor (50) (Figure 6). These findings suggest that the pathological ER aggregation observed with ADNDI mutants represent an aberrant, mislocalised process that physiologically occurs in granule biosynthesis, supporting the "functional amyloid" hypothesis.

7. ER-associated degradation plays a physiological role in water homoeostasis

Recently, the unexpected observation was made that mice with inducible deficiency of the essential ERAD components Sel1L or Hrd1 (Figure 4), developed polyuria and polydipsia due to DDAVP-sensitive DI (86). Endogenous pro-AVP was retained in the ER in these animals and the phenotype manifested without initial neuronal cell death. In Sel1L-deficient mice (Figure 7) as well as in cultured cells lacking Sel1L or Hrd1, wild type pro-AVP formed the same fibrillar, ER-associated disulfide-linked aggregations as ADNDI mutants. These findings show that pro-AVP is a physiological ERAD substrate, confirming and extending earlier findings of proteasomal degradation of mutant and wild type pro-AVP (73) and demonstrating the role of ER-associated degradation in maintaining physiological fluid homoeostasis. If transferred to the human, the data from mouse studies and experiments with cultured cells suggest that in ADNDI the capacity of the degradation machinery in vasopressinergic cells seems to be exceeded.

8. Conclusion

To differentiate the various aetiologies of the polyuria/polydipsia syndrome, clinical characteristics, personal and family history of affected individuals along with laboratory testing are key. In any person presenting with DI and a positive family history or childhood onset, even in the absence of affected family members, genetic analysis should be performed, focusing primarily on the *AVP* - , *AVPR2-* and *Aquaporin 2* – genes. Several varieties of hereditary neurohypophyseal DI exist, of which the autosomal-dominant form is by far the most common.

Practice Points

- Autosomal dominant neurohypophyseal DI manifests in childhood, and symptoms develop gradually
- In contrast, acute dehydration in the perinatal and infant period may be life-threatening in congenital nephrogenic DI

- Polyuria and polydipsia are the main clinical manifestations, but failure to thrive and mental retardation may result from repeated episodes of dehydration in children with untreated DI of any aetiology
- Always seek genetic testing (sequence analysis of the *AVP* - , *AVPR2-* or *Aquaporin 2* – genes, depending on clinical characteristics) if a positive family history and/or childhood manifestation is present

Research Agenda

- Study the role of ERAD in the pathogenesis of other disorders associated with protein aggregation
- Evaluate treatment options for such diseases by enhancing ERAD capacity
- Identify the mechanism of cell death and role of autophagy in ADNDI
- Identify the gene causing X-linked neurogenic DI
- Characterize the pathomechanism in neurohypophyseal DI associated with PCSK1 mutations.

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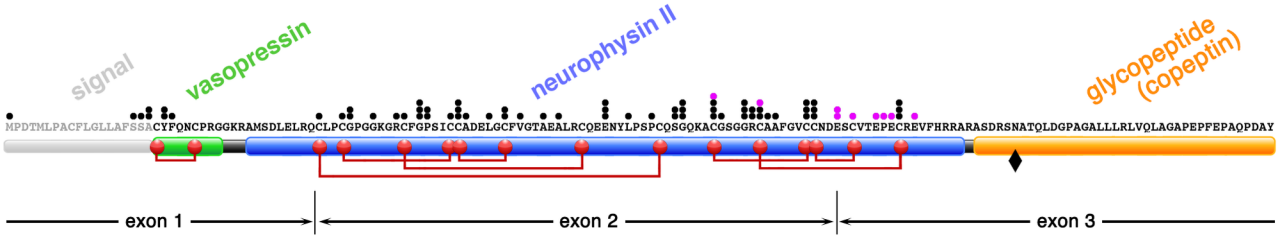
* Asterisked for particular relevance.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neurophysin II
glycopeptide
(copeptin)
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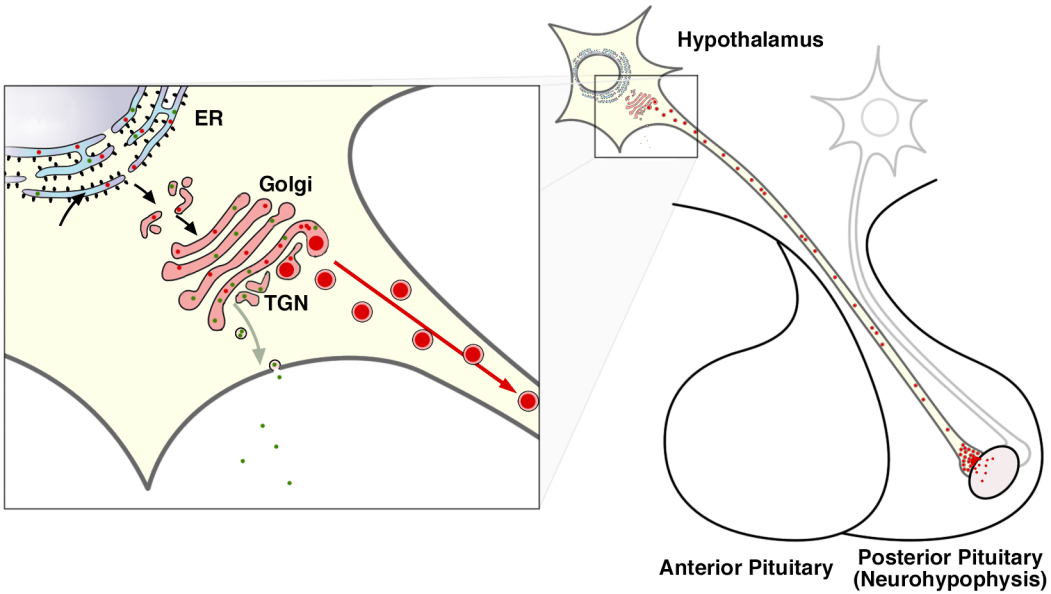
exon 1
exon 2
exon 3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TGN
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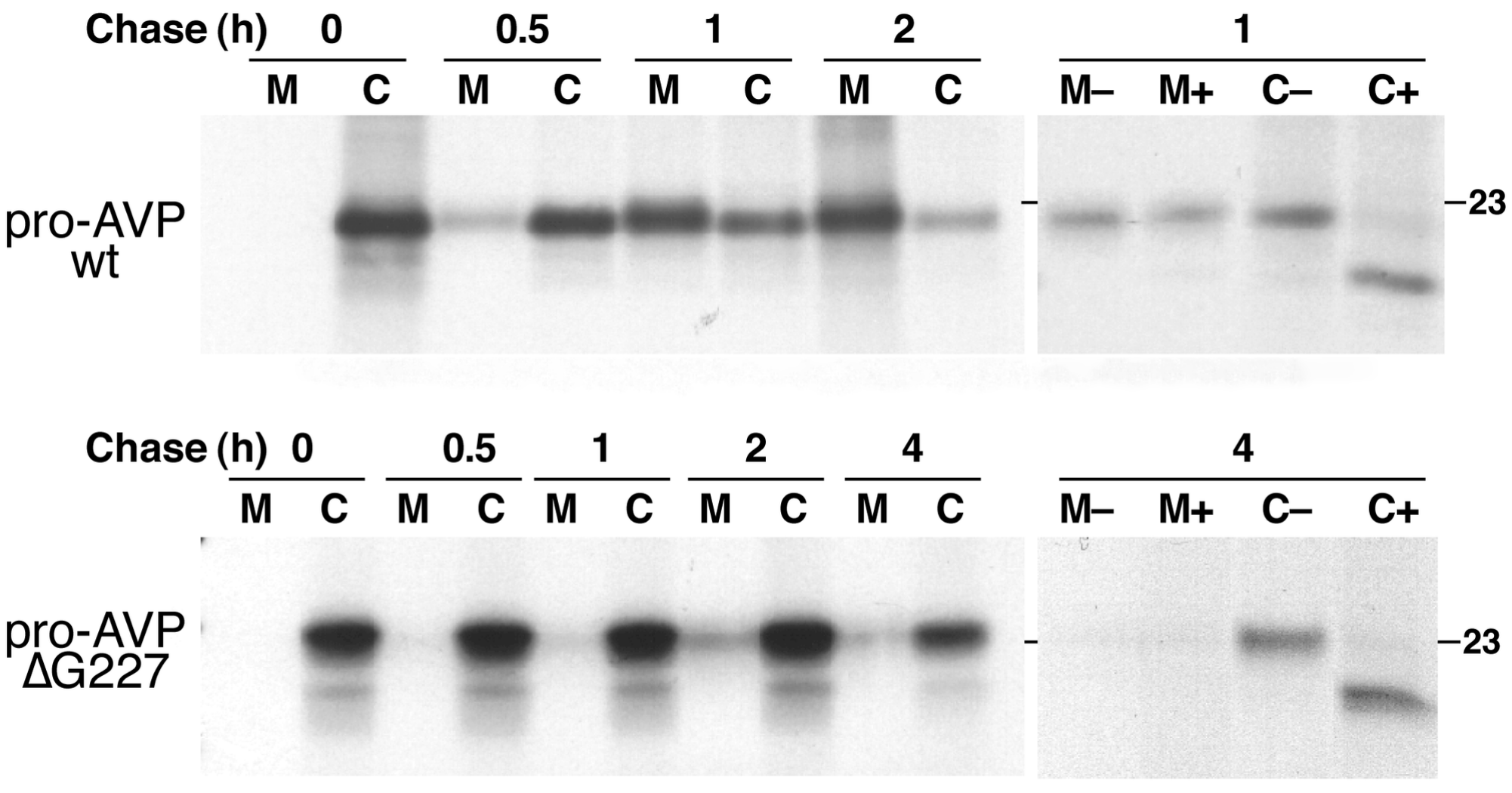
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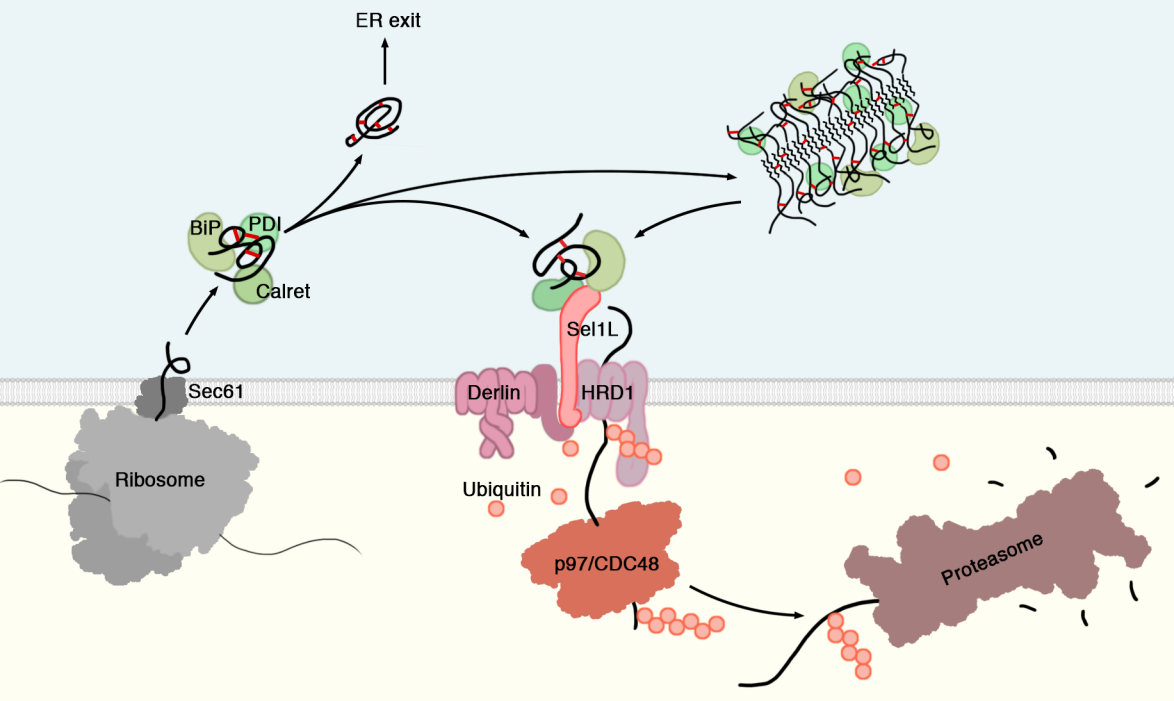
23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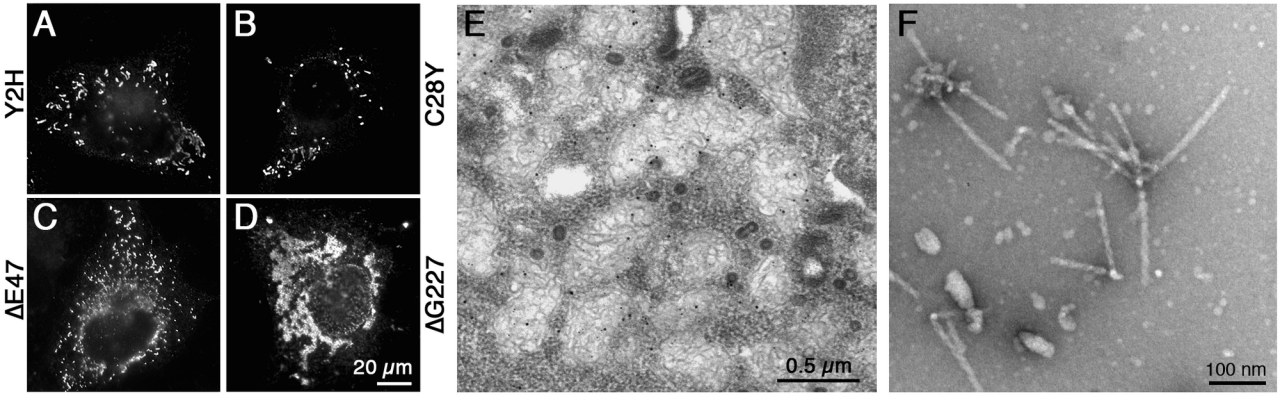
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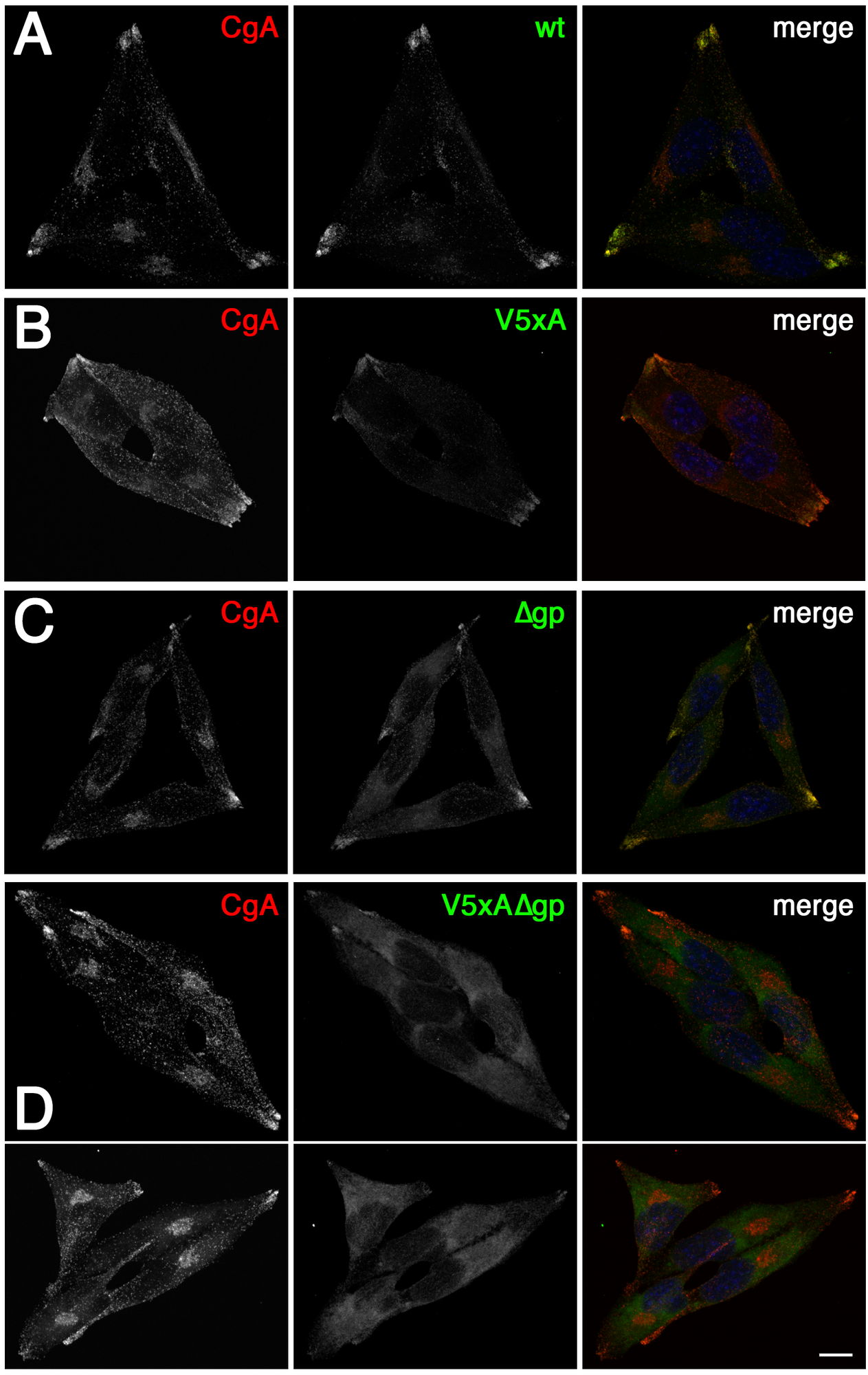
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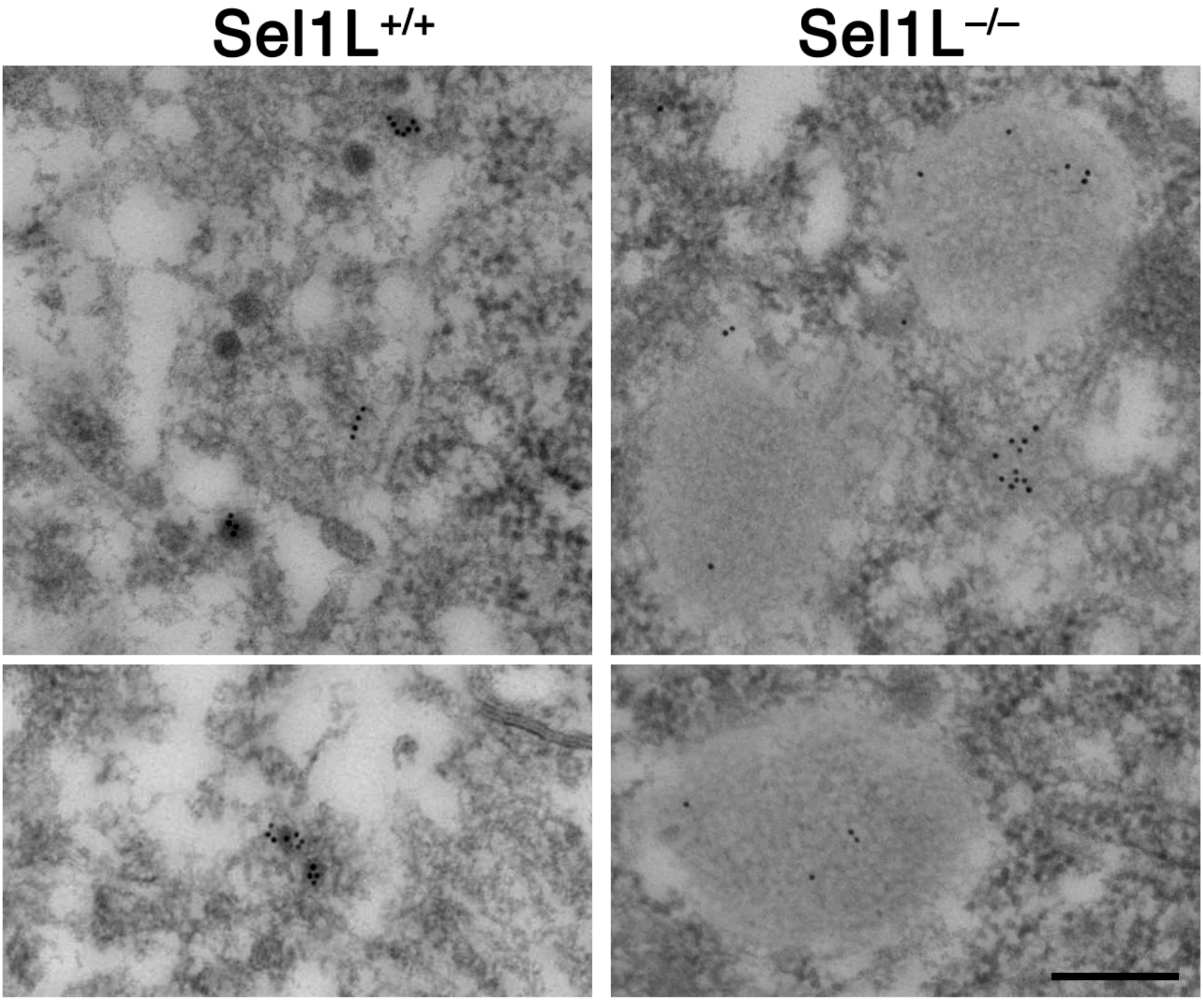
Sel1L+/+
Sel1L−/−

Table 1: Differential diagnosis of diabetes insipidus

DI type	Causes
Neurohypophyseal	• Trauma, including operations • Granulomatous disorders (sarcoidosis, histiocytosis) • Neoplastic disease (e.g. malignant metastases, germinoma, craniopharyngeoma, pituitary adenoma) • Infections • Ischemia (e.g. Sheehan's syndrome) • Brain edema (e.g. brain death) • Hemorrhagia • Autoimmune disease (e.g. neurohypophysitis, Lupus erythematodes) • Congenital malformations • Hereditary • Idiopathic
Renal	• Ischemia (e.g. tubular necrosis; sickle cell crisis) • Infiltrating disorders (e.g. amyloidosis, sarcoidosis) • Drug-induced (e.g. Lithium; Aminoglycosides, Cisplatin) • Hypokalaemia • Hypercalcaemia • Postobstructive (transient tubular damage) • Malignancy • Hereditary • Idiopathic
Primary Polydipsia	• Increased thirst (dipsogenic; e.g.meningitis, sarcoidosis, multiple sclerosis) • Excessive habitual drinking (psychogenic; e.g. schizophrenia, obsessive-compulsive disorder)
Gestational	• Increased AVP degradation by placental vasopressinase

Table 2: Forms of hereditary diabetes insipidus

DI type	Affected Gene	Chromosomal Location	Mode of Inheritance	OMIM* Entry
Neurohypophyseal	AVP (Antidiuretic hormone)	20p13	• Autosomal dominant (most common) • Autosomal recessive** (very rare)	125700; 192340
	Unknown	Xq28	• X-linked	n.l.***
	WFS-1 (Wolframin)	4p16.1	• Autosomal recessive	222300
	PCSK1 (Prohormone Convertase Subtilisin/ Kexin-type 1)	5q15	• Autosomal recessive	162150; 600955
Nephrogenic	AVPR2 (AVP type 2 receptor)	Xq28	• X-linked (most common)	304800
	AQP-2 (Aquaporin-2)	12q13.12	• Autosomal dominant • Autosomal recessive	107777

* OMIM; Online Mendelian Inheritance in Man®; https://omim.org
** the recessive mutation P7L (reference {Willcutts, 1999 #73}) is listed in OMIM entry 192340
*** n.l.; not listed