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REVIEW

p600/UBR4 in the central nervous system

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Abstract A decade ago, the large 600 kDa mammalian protein p600 (also known as UBR4) was discovered as a multifunctional protein with roles in anoikis, viral transformation and protein degradation. Recently, p600 has emerged as a critical protein in the mammalian brain with roles in neurogenesis, neuronal migration, neuronal signaling and survival. How p600 integrates these apparently unrelated functions to maintain tissue homeostasis and murine survival remains unclear. The common molecular basis underlying many of the actions of p600 suggests, however, certain conservation and transposition of these functions across systems. In this review, we summarize the central nervous system functions of p600 and propose new perspectives on its biological complexity in neuronal physiology and neurological diseases.

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Abbreviations

a.a.	Amino acid
ASD	Autism spectrum disorder
BPV-1	Bovine papillomavirus type 1
Ca^{2+}	Calcium
CaM	Calmodulin
CaMKIIα	CaM-dependent protein Kinase II α isoform
CNS	Central nervous system
ER	Endoplasmic reticulum
FAK	Focal adhesion kinase
hCALO	Human homologue of Calossin
HPV-16	Human papillomavirus type 16
MT	Microtubule
N-cadherin	Neuronal cadherin
p600	Protein 600
RB	Retinoblastoma protein
RBAF600	Retinoblastoma-associated factor of 600 kDa
Ub	Ubiquitin
UBR4	Ubiquitin protein ligase E3 component N-recognin 4
ZUBR1	Zinc finger UBR1 type 1

Introduction

Analysis of human brain cDNA libraries identified p600/UBR4 as a putative large protein enriched in the central nervous system (CNS) with undefined function [1–3]. In *Drosophila melanogaster* and *Arabidopsis thaliana*, the homologs of mammalian p600, Calossin/Pushover and BIG were characterized as a calmodulin (CaM)-binding protein/effector of neuronal excitability and regulator of the action

of the plant hormone auxin, respectively [4, 5]. Mammalian p600 protein was first investigated a decade ago. The name p600, advanced by Nakatani et al. [6], refers to the ~600 kDa size of the polypeptide. Based on the context of study, mammalian p600 is alternatively known as UBR4 (ubiquitin protein ligase E3 component N-recognin 4) [7], ZUBR1 (zinc finger, UBR1 type 1), RBAF600 (retinoblastoma-associated factor of 600 kDa), or hCALO (human homologue of Calossin) [8].

In their work on the N-end rule degradation pathway (for reviews see [9–11]) of the ubiquitin (Ub)-mediated proteasomal system, the Kwon laboratory identified UBR4 as an atypical member of the UBR box family of E3 Ub ligases [7]. This family of single RING finger E3 Ub ligases is characterized by an ~70 a.a. UBR box target-recognition motif (see [7, 9]). Unlike other UBR box family members (UBR1-3, UBR5-7), p600 does not contain any characterized E3 Ub ligase domains. In an independent study, Nakatani and colleagues [6] revealed that p600 is a retinoblastoma protein (RB)- and CaM-associated protein with potential roles in cell adhesion, particularly in the context of anoikis, a form of apoptosis induced by cell detachment. At the same time, the Munger and Howley [12, 13] laboratories discovered that p600 constitutes a novel target of the viral transforming factor E7 from human papillomavirus type 16 (HPV-16) and bovine papillomavirus type 1 (BPV-1), respectively, and suggested viral co-option of p600 functions in virus-induced cancers. This particular area of research has recently been revisited [14–18] and is paralleled by evidence of a role of p600 in aberrant cell invasiveness and survival [19].

Through our research on cytoskeletal proteins, we have studied roles of p600 in the brain. Here, we will primarily review the CNS roles of p600 in neurogenesis, neuronal migration, neuronal signaling and survival [20–23], and discuss their potential implications for human neurodevelopmental and neurodegenerative disorders.

p600 expression in the brain

The human *p600* gene is located on the complement strand at 1p36.13, whereas the mouse *p600* gene is found on the forward strand of chromosome 4. The canonical human p600 protein contains 5183 a.a., while its canonical mouse counterpart is a 5180 a.a. polypeptide, sharing 97 % identity and 98 % similarity, respectively. While a number of protein-coding mRNA splice variants have been identified for both human and mouse p600 (Ensembl; http://www.ensembl.org/), their specific distribution has neither been examined to date, nor have they been systematically characterized. Given that alternative splicing is typically highest in the brain [24], a comprehensive study of neuronal p600 splice variants represents an important future avenue of research. The potential existence of neuron-specific isoforms that would preclude to the full range of binding domains may contribute to specific p600 neuronal functions.

At the protein level, p600 is ubiquitously expressed in all tissues at variable levels, but is highly enriched in the CNS (i.e., brain and spinal cord) [7, 20, 22]. In the mouse brain, p600 protein is detected at embryonic day 12.5 and reaches maximal levels during adulthood [20]. In the adult brain, it is expressed roughly throughout a dozen brain regions, such as the cortex, thalamus, hypothalamus (including suprachiasmatic nucleus), and limbic structures [20–22] that have been associated with specific animal behaviors such as learning and memory and circadian rhythm (see below, for a general review see [25, 26]).

p600 protein domains

Human p600 contains several identified functional domains (Fig. 1). p600 displays a well-characterized 63 a.a. conserved UBR box motif (a.a. 1662–1724) [7]. The C-terminal region of p600 (a.a. 3214–5183) encompasses at least two microtubule (MT)-binding domains [20]. These MT-binding regions do not exhibit sequence homology to known MT-binding motifs (e.g., the MT-binding repeats of the MAP2/Tau family [27]). One of p600's MT-binding domains is hypothetically situated in proximity to one of two endoplasmic reticulum (ER)-binding regions (a.a. 3214–3899). A second ER-binding region is located near the center of the protein (a.a. 1681–2401) [20]. p600 also contains an interaction domain for the small atypical MT-associated protein Ndel1 (a.a. 4480–5183, possibly within a.a. 4480–4949) [22]. Finally, p600 possesses an atypical CaM-binding domain (a.a. 4076–4112) [21]. In contrast to the 1:1 CaM-to-target ratios of the canonical CaM-binding motifs [28], this CaM-binding domain mediates both 1:2 and 1:1 CaM-p600 binding ratios and does not exhibit sequence homology to other known CaM-binding domains [21]. These MT, Ndel1, CaM, and ER-binding regions have been characterized by our research groups in the context of p600 brain functions (see below). To date, the secondary and tertiary protein structures of p600 have not been elucidated. A truncated fragment of the C-terminal region of p600 is capable of dimerization in vitro, but it is unclear if such dimerization occurs with full-length p600 in vivo [22].

The roles of p600 in the CNS

The formation of the brain commences with the establishment of the neural tube followed by the lateral

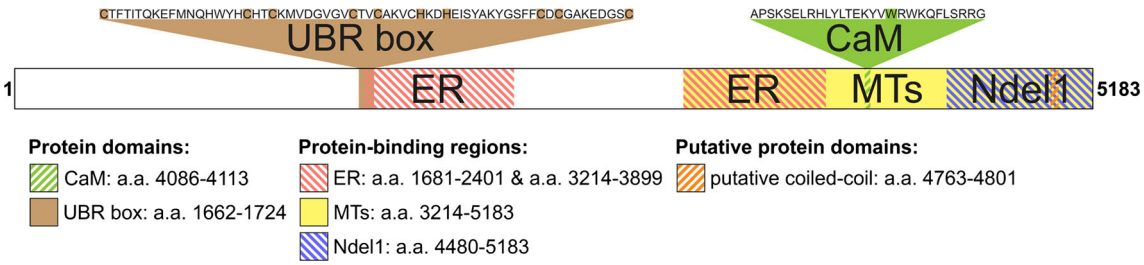

Fig. 1 Protein domains and protein-binding regions of p600. p600 contains a 'UBR box domain' with conserved cysteine (C) and histidine (H) residues (*shaded* in *brown*) [7]. These key residues are thought to hold three zinc ions in place, providing substrate specificity and stabilizing the UBR box structure [108, 109]. p600 also displays an atypical CaM-binding domain with a key residue, W4103 (*shaded* in *green*), that, once mutated, abolishes the interaction with CaM [21]. The C-terminal of p600 contains a large MT-binding region with likely at least two separate MT-binding domains [20]. The MT-binding region overlaps with the Ndel1-binding region (*blue*) [22] and one of the two ER-associated regions (*red*) [20]. The second ER-associated domain is located in a more N-terminal region of the protein. Finally, a putative 39 bp coiled-coil domain, predicted by the structural prediction tool MARCOIL at a 50 % probability threshold (v1.0, Max–Planck Gesellschaft) (http://bcf.isb-sib.ch/Delorenzi/Marcoil/index.html), is located within the Ndel1-binding region. This putative domain may mediate the direct interaction with the Ndel1 coiled-coil domain [22]

expansion of neural progenitors. Post-mitotic neurons arising from neural progenitors then migrate to their final destination where they form synapses with neighboring counterparts, thereby integrating into networks of connections that will be activated upon a specific stimuli or behavior (such as light or learning and memory) (see [29–35]). Proper activation of the networks maintains neuronal survival and brain homeostasis. p600 plays important roles in neural progenitors and post-mitotic neurons throughout brain development and maturity [7, 20–23]. In the next sections, we will detail the actions of p600 in the CNS and discuss its potential implication in brain health and diseases (a summary of the known CNS and non-CNS functions of p600 is shown in Fig. 2).

p600 in neurogenesis

Neurogenesis is the process that generates new neurons in the developing and adult brain. During pre-natal development, the bulk of neurogenesis occurs within proliferative zones located along ventricles [36, 37]. Populations of neural progenitors in these niches (i.e., ventricular zones) expand, and over time differentiate into neurons (for a review, see [29–32]). Our recent study demonstrates that p600 contributes to neurogenesis in the developing neocortex [22]. This contribution was revealed by the analysis of the orientation of the mitotic spindle [22], a correlative measure to the choice of neural progenitors to proliferate or differentiate, and significantly influencing neural progenitor survival [38, 39]. During the proliferation phase, the mitotic spindle in neural progenitors is oriented horizontally relative to the apical surface of the niche (i.e., ventricular zone). During the later neuronal differentiation phase, the fraction of neural progenitors with obliquely/vertically oriented spindle in the ventricular zone increases [40, 41]. In neural progenitors depleted of p600 by siRNA or knockout for *p600*, the mitotic spindle is preferentially tilted obliquely/vertically [22]. This tilting correlates with faster terminal neuronal differentiation of neural progenitors, premature depletion of progenitors and overall decreased production of neurons. Our study suggests that p600 regulates spindle orientation through a direct interaction with Ndel1 [22] (a protein with roles in neurogenesis, and mitotic spindle orientation of ventricular zone neural progenitors [42–44]), possibly via association with the lissencephaly-1 gene product Lis1, thereby modulating the function of the Dynein motor in anchoring astral MTs to the cell cortex (see [44–46] for further details on the Lis1/Dynein-dependent mechanism of astral MTs anchorage). This idea is compatible with the MT-associated protein nature of p600 [20] and its presence in mitotic spindle preparations from CHO cells [47].

Interestingly, poor cell–cell contact maintenance has been reported for p600-depleted fibroblasts in culture [6]. Furthermore, neural progenitors lacking p600 in the ventricular zone display diffuse and uneven staining of N-cadherin (Fig. 3) reminiscent of neural progenitors of Lis1 mutant mice (see Figure 6 of Pramparo et al. [44]). As alterations in cadherin-mediated cell–cell adhesion have been linked to neurogenic defects (see the review [48]), p600 may also contribute to embryonic neurogenesis via cell adhesion mechanisms. This hypothesis would be compatible with several studies in other tissues showing that cell adhesion molecules can orient the mitotic spindle during cell division [49–52].

Despite p600's implication in neurogenesis, there is only limited evidence of a role of p600 in cell cycle progression. Previously, p600 has been shown to complex with cyclin E and A constructs [53] as well as the nuclear-localizing RB protein [6] that plays a central role in cell cycle progression

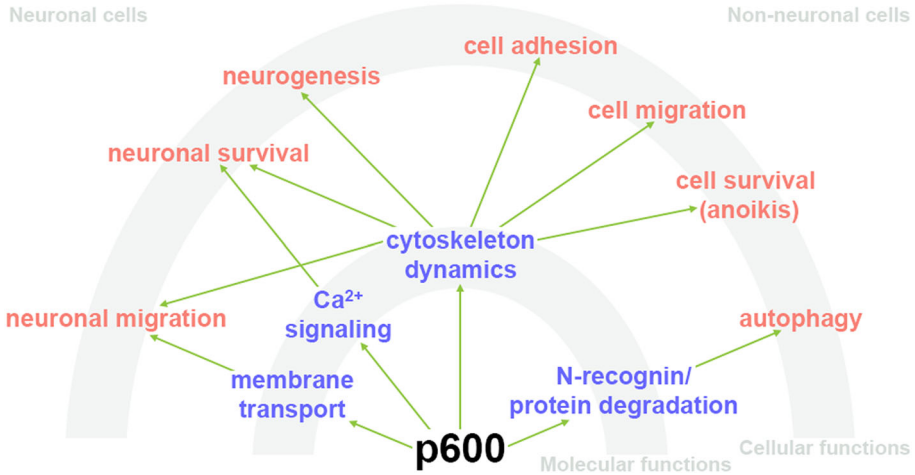

Fig. 2 Molecular and cellular functions of p600 in neuronal and non-neuronal cells. The molecular functions of p600 that underlie its cellular functions are indicated in *blue*. The cellular functions identified in neuronal cells are shown on the *left*, while those identified in non-neuronal cells are shown on the *right*. The illustrated links between the molecular and cellular functions have been demonstrated experimentally. Many other cross-associations of functions are likely to exist but have not been demonstrated experimentally to date

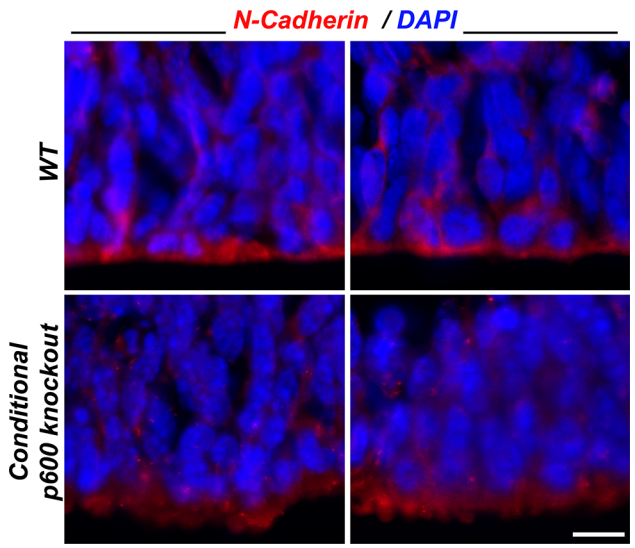

Fig. 3 N-cadherin staining in the cortical ventricular region of mice lacking p600 specifically in epithelial stem cells. N-cadherin is expressed in a tight pattern in neural progenitors lining the ventricular zone in the neocortex at embryonic day 12.5. In mice lacking p600 in epiblasts including neural progenitors (*p600 Sox2-Cre* conditional knockout) [22], the N-cadherin staining pattern is diffuse and irregular. N-cadherin (Cy3, *red*), DAPI (*blue*), *scale bar* 10 μm

[54]. Phosphorylation of p600 at a cyclin-dependent kinase consensus site also varies slightly in a cell cycle-dependent manner [53]. The significance of these interactions and phosphorylation events has, however, not been studied functionally and has not been linked to proliferation of neural progenitors. Further studies are required to link the spindle orientation and cell adhesion functions of p600 to its eventual role in cell cycle.

p600 in neuronal migration

Newly born immature cortical neurons migrate out of the ventricular niche to reach their final destination in the neocortex where they form synapses with their counterparts. The process of neuronal migration governs the inside-out layering of the brain, with earlier-born neurons passed by the later-born neurons (for reviews, see Refs. [33–35]). Migrating cortical neurons express p600 [20]. Depletion of p600 by siRNA impedes neuronal migration, leading to their accumulation near the ventricular zone (i.e., their mis-positioning in the developing brain) [20]. p600 shows all the classical features of a MT-associated protein (i.e., MT polymerization, MT stabilization and localization to MTs) but also exhibits the unique feature of binding the ER [20]. By maintaining the interface between MT and ER membranes, p600 may facilitate the transport of ER membranes on MTs. This is particularly important in the context of migrating cells, such as migrating neurons in the developing cortex, that require localized distribution of ER membranes for localized calcium (Ca^{2+}) signaling and cytoskeletal remodeling. p600-depleted neurons exhibit thin, crooked and zigzag leading processes with few ER membranes [20]. This alteration likely explains the defects in migration as migrating neurons require a strong robust leading process filled with dynamic MTs to pull centrosome and nucleus toward the direction of migration and to localize ER membranes for localized Ca^{2+} signaling and cytoskeletal remodeling in situ. In sum, p600 is proposed to interface MT dynamics and ER transport/signaling to promote neuronal migration. By virtue of its regulation of the activity of Focal Adhesion Kinase (FAK) and its co-

localization with F-actin [6, 55], a role for p600 in actin dynamics during neuronal migration cannot, however, be excluded.

p600 in neuronal Ca^{2+} signaling and neuronal survival

While p600 confers resistance to apoptosis induced by cell detachment (termed anoikis), it also promotes cell survival through other mechanisms independent of cell adhesion. At low confluence where cells receive lower survival signals from neighboring cells, or in serum-free media, depletion of p600 triggers an exponential increase in levels of apoptosis [6]. These results suggest that p600-depleted cells have a greater requirement for ongoing survival signals such as trophic factors. New mechanistic insights into the anti-apoptotic roles of p600 may come from a number of p600-interacting proteins recently identified by immunoprecipitation/mass spectrometry. These include the anti-apoptotic proteins c-IAP1 and c-IAP2 that modulate various stress/inflammatory responses [56, 58] as well as an Ei24 construct [59], a pro-apoptotic factor participating in p53-mediated apoptosis [60–62]. The p53-dependent death pathways involving RB phosphorylation have been characterized in several neuronal populations [63]. Since p600 binds to RB [6], it may play a role in p53-induced apoptosis. Whether p600 counteracts cell death signals destined to the apoptosome remains an open question.

Mature post-mitotic neurons become active upon binding of neurotransmitter to their receptor and depolarization (excitation). Our recent study in post-mitotic primary hippocampal mouse neurons demonstrated that p600 promotes neuronal survival under ambient neuronal activity and upon glutamate-induced excitotoxic conditions, i.e., over-activation/overexcitation of neurons through Ca^{2+} dyshomeostasis, independent of its MT-associated function [21]. Precisely, depletion of p600 by RNAi significantly increases the proportion of neurons showing CaM-dependent protein Kinase II α isoform (CaMKIIα) aggregation, a proxy of neuronal death, upon glutamate-induced Ca^{2+} entry in hippocampal cultured neurons. Interestingly, p600 was found to form a complex with CaM and CaMKIIα, mediated by a direct and atypical interaction between p600 and CaM. Specific disruption of this interaction using a blocking peptide resulted in neuronal death under ambient activity, and potentiated CaMKIIα aggregation following application of mild doses of exogenous glutamate. In this experimental setting, neurons lacking p600 do not undergo demise by apoptosis but most likely die by autophagy, a key role advanced for p600 in the mesoderm of the yolk sac [64]. Interestingly, when single neurons are depolarized directly by photoconductive stimulation (for an overview of this technology, see [65]), p600 harnesses its MT-associated protein function to prevent CaMKIIα aggregation. The effectiveness of MT stabilization in preventing CaMKIIα aggregation during direct depolarization, but not during glutamate treatment, suggests a model wherein p600 has two modes of survival action depending on the source of cytosolic Ca^{2+} [21]. The ability of p600 to handle Ca^{2+} signals may be related to the Ca^{2+} transducer function of its *Drosophila melanogaster* homolog Calossin/Pushover during neuronal depolarization and neurotransmitter release [4].

The unequivocal proof for a fundamental role of p600 in cell and neuronal survival is illustrated by the numerous phenotypes displayed by three *p600* knockout mouse models. These mice have pleotropic tissue defects characterized by necrotic, apoptotic and autophagic degeneration, and early embryonic lethality (see Table 1 for details; Tasaki et al. [64]; Nakaya et al. [55]; Belzil et al. [22]). Whether the requirement for p600 in survival in different tissues (i.e., yolk sac, heart, liver, brain, etc.) originates from loss of a single or several functions described for p600 remains to be determined. This question could be addressed by the generation of knock-in mice of p600 lacking specific protein domain(s) associated with a particular function. Similarly, *p600* null tissues and cells may display certain selectivity in regard to their propensity to degenerate and die by apoptosis, necrosis, or autophagy. Taken together, p600 appears to exhibit several pro-survival roles per se that could prevent necrosis, regulate autophagy, or counteract apoptosis depending on the challenge type and duration.

A putative role of p600 in the degradation of neuronal proteins

Like in non-neuronal cells, misfolded, damaged, or redundant proteins are degraded in neurons via the Ub-mediated proteasomal system, where ubiquitination is used to target specific proteins to the proteasome. The process of ubiquitination occurs over a sequence of enzymatic steps, with final Ub transfer to target proteins mediated by the E3 Ub ligases (see [66]). In contrast, bulk polypeptides or whole organelles are degraded through autophagy, where membrane-enveloped targets are degraded by lysosomal enzymes (see Ref. [67]). While upregulated in adverse conditions, like the Ub-mediated proteasomal system, autophagy is critical in ongoing cell and tissue homeostasis [68]. Remarkably, p600 functions in *both* protein degradation pathways in non-neuronal cells and tissues [7, 69–71], suggesting that it could perhaps mediate the same functions in neurons.

A potential role of p600 in protein degradation in the CNS is supported by the characterization of knockout animals for other UBR family members. For instance,

Table 1 p600 knockout and in utero electroporation mouse models

Mouse model	Strategy used to generated KO	Tissues targeted by KO	Age of embryonic lethality	Phenotypes	References
p600 gene deletion models					
p600 null (C57BL/6J:129/Ola)	*p600* exon 36–42 deletion; no truncated forms detected but plausible	All tissues (embryonic/extra-embryonic)	≥E9.5 to <E11.5	Yolk sac detects Growth retardation	Tasaki et al. [64]
p600 null (C57BL/6)	*p600* exon 1 deletion; no side-products/truncated forms noted	All tissues (embryonic/extra-embryonic)	E11.5 to <E13.5	Growth retardation Placenta detects	Nakaya et al. [55]
p600 conditional null (C57BL/6)	Deletion *p600* exon 1 using *Sox2-Cre*; no side-products/truncated forms noted	<E6.5, embryo proper and epiblast-derived extra-embryonic layers	≥E12.5 to <E14.5	Growth retardation Placenta detects Liver defects CNS defects: Randomized neural progenitor spindle orientation; decreased neurogenesis; increased, apoptosis	Nakaya et al. [55], Belzil et al. [22]
In utero cortical electroporation models					
p600 RNAi in utero electroporation	RNAi sequence: GCAGTACGAGCCGTTCTAC and AATGATGAGCAGTCATCTA	Electroporation at E13, analysis at E14 or E15	N/A	CNS defects: randomized neural progenitor spindle orientation; premature neuronal differentiation	Belzil et al. [22]
p600 RNAi in utero electroporation	RNAi sequence: GCAGTACGAGCCGTTCTAC and AATGATGAGCAGTCATCTA	Electroporation at E14, analysis at E17	N/A	CNS defects: neuronal migration defects	Shim et al. [20]
Human $p600^{4480–5183}$ fragment in utero eletroporation	Construct of human p600 a.a. 4480–5183	Electroporation at E13, analysis at E14, E15	N/A	CNS defects: randomized neural progenitor spindle orientation; premature neuronal differentiation	Belzil et al. [22]

defects in embryonic neurogenesis were reported in double knockout *Ubr1*/*Ubr2* [72] and single *Ubr5* null [73] mice. Furthermore, sensory neuronal deficits (loss of hearing and smell) were reported for *Ubr3* null and heterozygous *Ubr6* knockout mice [74, 75]. Interestingly, p600 is also a time-of-day-dependent and light-inducible protein in the suprachiasmatic nucleus of the mouse brain during circadian rhythm [76], a complex biological process that comprises the physical, mental and behavioral changes in an organism in response to light and darkness during a 24-h cycle. During circadian rhythm, a set of "clock" proteins are tightly expressed (for a review see [77, 78]). By virtue of its role in protein degradation and its circadian pattern of expression, p600 may be a candidate of choice to regulate clock protein degradation in the suprachiasmatic nucleus [76].

In the context of neurodegeneration, the aggregation of CaMKIIα in p600-depleted neurons suggests that p600 is important for protein degradation in nerve cells undergoing challenges [21]. Furthermore, the PARKIN-recruiting protein PINK1 has been identified among the targets recognized and degraded via p600 [71]. Interestingly, mutations in both PARKIN and PINK1 have been found in patients with Parkinson's disease [79] but their relationship to p600 in Parkinson's disease remains unknown. Finally, in humans, other UBR box family proteins are associated with disorders such as Johansson Blizzard Syndrome (a disease typically associated with varying degrees of intellectual disability, and sometimes, structural CNS anomalies) as well as epilepsy and autism spectrum disorder (ASD) [80–83]. Thus, the potential role of p600 in protein degradation in neurons is intriguing and warrants further investigation.

p600 in neurodevelopmental and neurodegenerative diseases?

In the developing brain, p600 plays an important role in cortical neurogenesis [22] and cortical neuronal migration [20]. These functions may be linked to p600's interaction with Ndel1, a cytoskeletal protein with reduced expression in schizophrenia [84] and associated with a wide spectrum of neurodevelopmental disorders including lissencephaly, intellectual disability, autistic behaviors, and AD/HD through interactions with Lis1 and DISC1 [85–92]. As both neurogenesis and neuronal migration are all important in the pathophysiology of neurodevelopmental disorders, loss of p600 functions may contribute to neurodevelopmental disorders through these altered processes.

Within the general population, genes associated with developmental disorders numerically tend to show relatively low rates of functional variation (e.g., missense mutations). Disorders such as intellectual disability, ASD, and epileptic encephalopathies correlate with enrichment in *de novo* functional mutations in these intolerant genes [93]. The human *p600* gene shows numerically very little tolerance to functional variation in the general population [93], suggesting that perhaps, its alterations are associated with neurodevelopmental defects. In support of this idea, a literature search [94, 95] combined with databases such as DECIPHER (http://decipher.sanger.ac.uk/) and dbVar (http://www.ncbi.nlm.nih.gov/dbvar/) [96–100] revealed a number of human cases with *p600* copy number variation including cases featuring neurodevelopmental defects (Fig. 4). Further investigation is needed to determine whether these *p600* copy number variations are incidental, contributors or modifiers of neurodevelopmental diseases.

Ca^{2+} dyshomeostasis, cytoskeletal collapse, and protein aggregation are common features of acute and chronic neurodegeneration [101–104] and found in neurons with altered p600 functions [21, 23]. By virtue of p600's roles in Ca^{2+} signaling, cytoskeleton stabilization, and protein degradation, alterations in p600 may contribute to neurodegenerative conditions. In support of this view, levels of p600 at neuron synapses decrease in mouse models of Huntington's disease, spinocerebellar ataxia, and neuronal injury [105]. Interestingly, *p600* was recently identified as a candidate loci in an autosomal dominant non-progressive early-onset episodic ataxia [106]. In the neuronal injury model, the decrease in p600 levels could be detected at both 24 and 48 h post-lesion, and therefore has been proposed to contribute directly to synaptic dysfunction and neurodegeneration observed at later stages [105]. Mass spectrometric analysis also detected changes in p600 levels in a mouse model of Parkinson's disease induced by the neurotoxin MPTP: a significant decrease was found in the cerebellum of these animals, whereas increased levels were seen in both cortex and striatum [107]. In brief, our understanding of the implication of p600 in neurodegenerative diseases remains at the preliminary stage. The generation of mice overexpressing or lacking p600 in specific brain regions combined with human genetic and biochemical studies will help to elucidate the potential roles of p600 in neurodegenerative diseases.

Conclusion

Over the last decade, significant advances have been made on the roles of p600 in mitotic and post-mitotic cells and tissues. For instance, our understanding of the importance of p600 in protein degradation and the identification of its targets has gained momentum. Similarly, co-option of several of p600's functions by viruses is being scrutinized. In our laboratory, we have contributed to unraveling the

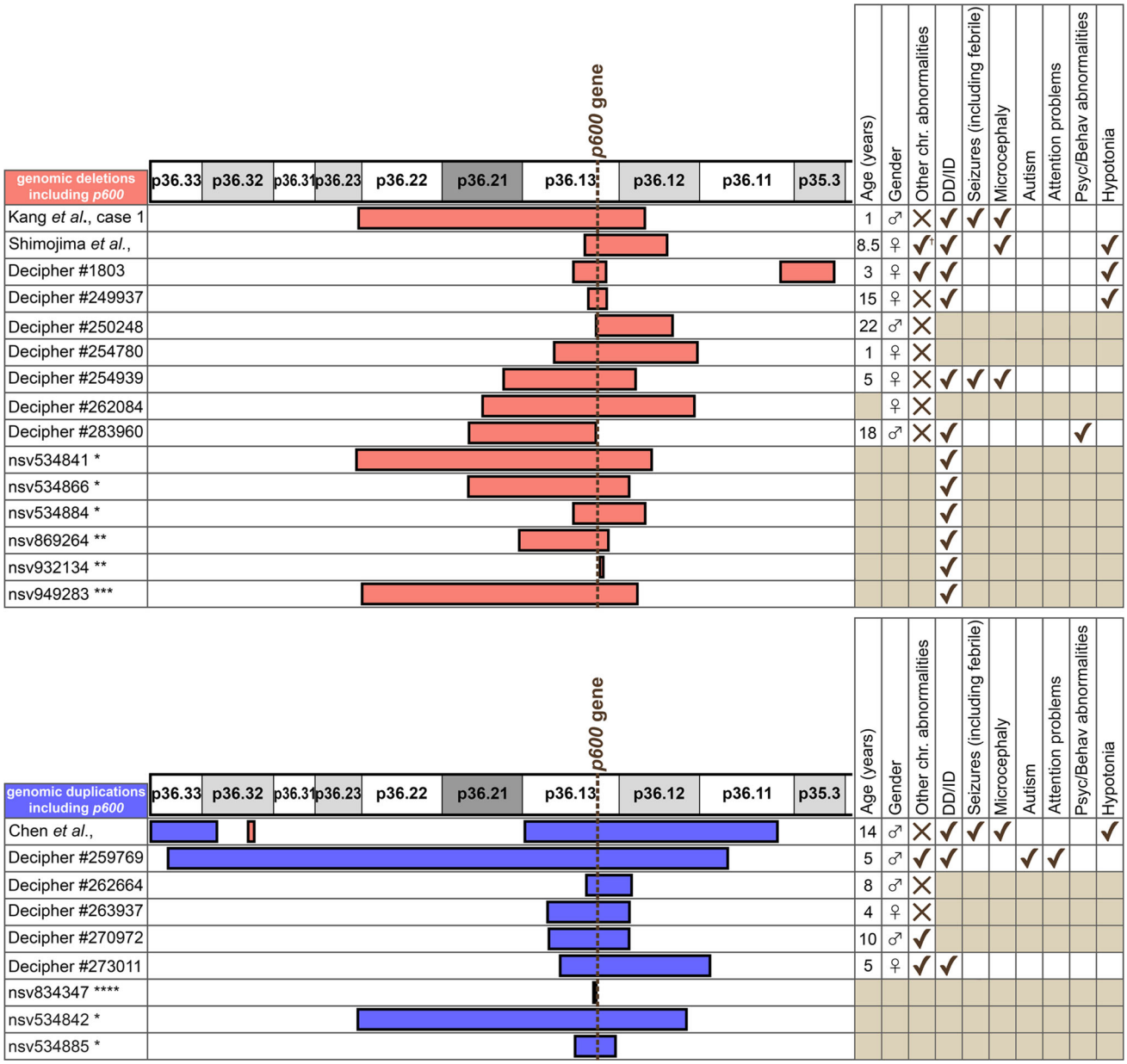

Fig. 4 Summary of copy number variations including the *p600* gene associated with human neurodevelopmental disorders. The location of the human p600 gene at 1p36.13 is indicated by the *vertical brown dashed line*. Genomic deletions including the *p600* gene are indicated in *red*. Genomic duplications including the *p600* gene are indicated in *blue*. For patient phenotype, *check mark* indicates the explicitly stated presence of a phenotype. *Cross mark* is used to denote the absence of further identified chromosomal abnormalities. *Brown shaded boxes* indicated the absence of patient information. *Cases included in Cooper et al. [96]; **cases included in Kaminsky et al. [97] and Miller et al. [98]; ***case included in Vulto-van Silfhout et al. [99]; ****case included in Wong et al. [100]. †The second chromosomal abnormality for the patient reported by Shimojima et al. [95] is a inv(3)(p14.1;q26.2), a region that does not contain any known genes, and is thus not thought to contribute to the phenotype of this patient. *chr* chromosomal, *DD* developmental delays, *ID* intellectual disability. This summary makes use of data generated by the DECIPHER Consortium. A full list of centers that contributed to the generation of the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Welcome Trust

CNS functions of p600 throughout brain development and maturation, but we are aware that much more work remains to be done. For instance, an exciting future area of study is the elucidation of the brain region-specific functions of p600. The enrichment of p600 in pyramidal neurons of the hippocampus suggests critical roles for the protein in establishing neuronal networks that could impact the process of learning and memory. Likewise, p600 may be

critical for degradation of clock proteins in the suprachiasmatic nucleus during circadian rhythm. Addressing these fundamental biological questions will eventually shed new light onto the implication of p600 in human neurological diseases.

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