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REVIEW ARTICLE

# *PRODH* variants and risk for schizophrenia

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**Abstract** Schizophrenia is a common, devastating neuropsychiatric disorder whose etiology is largely unknown. Multiple studies in humans and in mouse and fly models suggest a role for proline and *PRODH*, the gene encoding the first enzyme in the pathway of proline catabolism, in contributing risk for schizophrenia. Other studies, however, reach contradictory conclusions. Here, we provide a critical review of the data in the context of what is known about proline metabolism and suggest studies for the future. Overall, there is considerable evidence supporting a role for certain loss of function *PRODH* variants conferring risk for schizophrenia in some individuals.

**Keywords** Schizophrenia · Proline · *PRODH* · Hyperprolinemia I · Hyperprolinemia II

## Introduction

Proline is a nonessential, protein amino acid that, in addition to its role as a substrate for protein synthesis and a precursor of glutamate, has several properties suggesting it may function as an inhibitory neurotransmitter in a subset of glutamatergic synapses (Phang et al. 2001). In support of this hypothesis, a specific, high-affinity proline transporter (SLC6A7) has been shown to localize to membranes of subsynaptic vesicles and plasma membrane of certain glutamatergic neurons in the central nervous system (Renick et al. 1999; Shafqat et al. 1995). Proline is degraded to $\Delta^1$-pyrroline-5-carboxylate (P5C) in a FAD-dependent reaction catalyzed by proline oxidase (POX), an inner mitochondrial membrane enzyme expressed in kidney, liver and brain (Phang et al. 2001). P5C, in turn, can be converted to glutamate in a reaction catalyzed by P5C dehydrogenase or recycled back to proline in a reaction catalyzed by P5C reductase using either nicotinamide adenine dinucleotide phosphate or nicotinamide adenine dinucleotide as cofactors. The latter reactions, together with that catalyzed by POX, comprise a cycle of proline synthesis and degradation that transfers redox potential between the mitochondrial matrix and the cytosol or between cells (Phang et al. 2001). POX is encoded by *PRODH*, a gene spanning 23.8 kb with 15 exons and localized to 22q11.2 at 17.3 Mb.

Two astute observations led to the hypothesis that variation in *PRODH* may confer risk for schizophrenia (Sz). First, in 1994, following up on preliminary linkage data and overlapping phenotypic features, Pulver and her colleagues (Pulver et al. 1994; Karayiorgou et al. 1995) reported a dramatic (~25-fold) increased incidence of Sz in individuals with the DiGeorge/Velocardiofacial syndrome, a common (~1/4,000 live births), contiguous gene syndrome also known as 22q11DS (McDermid and Morrow 2002; Weksberg et al. 2007; Williams et al. 2006). Second, in 1996, well before genome sequence information was available, Jaeken et al. (1996) noted hyperprolinemia in a 22q11DS patient and suggested that the *PRODH* gene might be located in 22q11. We now know that both observations were correct and in what follows, we will review the evidence implicating *PRODH* in Sz.

## Nomenclature

The human genome contains two other genes with sequence similarity to *PRODH* that are designated in

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various ways in the public databases. One of these is a nonfunctional pseudogene (Ψ*PRODH*) that is the result of *PRODH* duplication. It is located 1.5 Mb more telomerically on 22q and has a structure similar to that of *PRODH* but with a complex internal deletion that extends from the 5′ end of intron 2 to the middle of exon 7 but retains a segment of intron 5 (Bender et al. 2005). Although Ψ*PRODH* does not encode a functional protein, it does appear to contribute to variation in *PRODH* by acting as a source for gene conversion events in which sequence variation accumulated in Ψ*PRODH* is transferred to *PRODH* (Bender et al. 2005; Liu et al. 2002b). The second *PRODH*-related sequence is located on 19q and encodes hydroxyproline oxidase (OHPOX), an enzyme that catalyzes the first step in hydroxyproline degradation and has little activity towards proline (Willis et al. in preparation). For clarity, we designate this gene *OHPRODH*.

## Schizophrenia

Schizophrenia (Sz) is a complex, chronic, debilitating neuropsychiatric disorder with an incidence of about 1% (Gogos and Gerber 2006; Harrison and Weinberger 2005; Lang et al. 2007; Norton et al. 2006; Ross et al. 2006; Sawa and Snyder 2002). Most affected individuals are relatively well until onset of symptoms, typically late in the second decade in males or in the third decade in females. Evidence for a genetic contribution to the etiology includes a 10-fold increased risk (~10%) for first-degree relatives of probands with Sz and an ~50% concordance rate for monozygotic twins. Multiple lines of evidence suggest that Sz is a developmental disorder of the nervous system with involvement of the glutamatergic synapses (Lang et al. 2007; Sawa and Snyder 2002). Aside from subtle reductions in the volume of the frontal lobes and other regions, there are no anatomical or histological abnormalities in Sz (Goldman et al. 2008; Ross et al. 2006). Several genes have been suggested to play a role in the etiology of Sz but few have been confirmed at the molecular level by demonstration of causative variants. The interested reader should see any of several recent reviews of the genetics of Sz (Gogos and Gerber 2006; Harrison and Weinberger 2005; Lang et al. 2007; Norton et al. 2006).

## Inborn errors of proline metabolism

There are two recognized monogenic inborn errors in proline degradation. Both are relevant for any consideration of a role for *PRODH* variants in Sz.

### Hyperprolinemia type I (HPI) (MIM 239500)

Originally described in 1961, type I hyperprolinemia (HPI) is an autosomal recessive disorder caused by deficiency of POX (Phang et al. 2001; Scriver et al. 1961). The phenotype of HPI has been considered benign or highly variable but, as described below, this view is under revision. Typically, plasma proline concentrations range from 500 to 2,200 μM (normal 51–271 μM) and there is no P5C detectable in urine. Because *PRODH* is not expressed in easily accessible cells or tissues and the molecular identification of *PRODH* is relatively recent, the diagnosis of HPI in most patients has been by exclusion rather than by direct enzymatic or molecular demonstration. It is likely that this lack of a diagnostic confirmation has contributed to confusion regarding the phenotypic significance of HPI.

### Hyperprolinemia type II (HPII) (MIM 239510)

HPII is an autosomal recessive disorder caused by deficiency of the second enzyme in the proline catabolic pathway, P5C dehydrogenase (Valle et al. 1976). On average, plasma proline levels in HPII are higher than those in HPI although there is overlap. HPII patients also excrete P5C in their urine and this biochemical marker distinguishes them from HPI. The clinical phenotype of HPII is variable: in there is an increased incidence of seizures, especially febrile seizures and some individuals have mild mental retardation. The disorder is rare and there is almost no information on the consequences of HPII in adults.

## Animal models

### *Drosophila*

In a screen of mutant flies with abnormal locomotor behavior, Benzer and colleagues identified one, designated *sluggish-A* (*slgA*) with a mutation in the fly ortholog of *PRODH* (Hayward et al. 1993). This important result provided sequence information useful for cloning mammalian *PRODH* genes and suggested POX deficiency and resultant hyperprolinemia could have a deleterious effect on CNS function.

### Mouse

The Pro/Re mouse is an inbred strain with hyperprolinemia and POX deficiency developed by >25 generations of sibling inbreeding from an original cross between 129/ReJ and C57BL/6J (Blake 1972; Blake and Russell 1972). Gogos and colleagues identified a *Prodh* nonsense mutation (E453X)

responsible for POX deficiency in the Pro/Re animals (Gogos et al. 1999). Using the *Prodh* mutation as a molecular marker, they crossed the original Pro/Re strain with C57BL/6J wildtype producing F3 animals that were either Prodh$^{-/-}$ or Prodh$^{+/+}$ and utilized them for anatomical, neurochemical and behavioral assays. The Prodh$^{-/-}$ animals had a 10-fold increase in plasma proline (60 vs. 600 μM), normal brain morphology and histology and modest (∼10–15%) but statistically significant reductions in glutamate, GABA and aspartate in hippocampus and frontal cortex. Interestingly, the Prodh$^{-/-}$ animals exhibited a significant reduction in prepulse inhibition (PPI), a neuropsychological response that is also reduced in humans with Sz (Braff et al. 1992).

In subsequent work, this same group improved their model by transferring the *Prodh*-E453X mutation into the 129/SvEv strain through 10 generations of backcrosses to minimize effects of genetic background differences (Paterlini et al. 2005). They utilized this POX-deficient inbred strain to perform additional behavioral, electrophysiological and molecular studies. They found the Prodh$^{-/-}$ animals exhibited enhanced glutamatergic signaling in the hippocampus. Baseline locomotor activity was reduced but could be dramatically enhanced by D-amphetamine administration as has been observed in individuals with Sz (Szaesko et al. 1999). Expression profiling of mRNA isolated from the frontal cortex of the Prodh$^{-/-}$ animals showed a striking increase, confirmed by RT-PCR, in the expression *Comt*, another gene in the 22q11DS critical region that has been implicated in Sz. Inhibition of COMT by administration of tolcapone, a reversible COMT inhibitor, accentuated the deficits in locomotor activity, working memory and PPI characteristic of the Prodh$^{-/-}$ animals. Based on these observations, the authors hypothesized that the induction of *Comt* expression in the Prodh$^{-/-}$ animals was a compensatory homeostatic response and theorized, on this basis, that the *COMT* genotype in humans may modify the phenotype of *PRODH* deficiency. *COMT* encodes catechol-*o*-methyltransferase, a key enzyme in the degradative pathway for several bioactive amines including dopamine (Williams et al. 2007). In humans, *COMT* has a common coding single nucleotide polymorphism (SNP), a G > A substitution (rs4680) that results in a V158M change in the protein. The G allele (V158) is more common with a frequency of 0.6–0.7 depending on the population and the V158 form of the protein has higher activity.

## *PRODH* variants and Sz

The observation of an ∼25-fold increased risk for Sz in individuals with 22q11DS as compared to the general population provided an important clue for the location of gene(s) contributing risk for Sz—a lamplight illuminating a 3 Mb segment or about 0.1% of the total length of the genome. Initial studies, based on the minimal overlap of a small number of 22q11DS individuals with Sz and variably sized deletions, narrowed the region of interest, the "critical region," to the centromeric 1.5 Mb of the typical 3 Mb 22q11DS deletion (Karayiorgou et al. 1995; McDermid and Morrow 2002). The 1.5 Mb critical region contains 27 genes with *PRODH* near the centromeric end and Ψ*PRODH* near the telomeric end.

Taking advantage of this "lamplight", Karayiorgou and her colleagues performed a scan of the region initially using 18 single nucleotide polymorphism (SNP) markers in 242 Sz patients and their families (Liu et al. 2002b). Their results showed two independent peaks of association, one at the centromeric end over the 3′ half of *PRODH* and the other at the telomeric end over a gene known as *ZDHHC8* (Karayiorgou and Gogos 2004; Liu et al. 2002a, b). Subsequent studies by three other groups, including 528 Chinese Sz families from China (Li et al. 2004), 93 Chinese Sz families from Taiwan (Liu et al. 2004) and 274 Ashkenazi Jewish Sz case-parent trios (Fallin et al. 2005), found similar or supporting results. Thus, the association of *PRODH* variants and Sz has been replicated in several different samples.

Although these results are provocative, several caveats must be mentioned. First, in their papers Liu et al. (2002a, b) surveyed a 1.5 Mb region association with what would now be considered a density of SNP markers that is low and could easily miss areas of significant association (∼1 SNP/20 kb) (Li et al. 2008). Currently, such studies would be done at a density about 10-fold higher (1 SNP/2 kb). Second, more recent and extensive mapping of the deletion breakpoints in a large series of Sz and non-Sz 22q11 DS patients identifies some with Sz in which the deletion is telomeric to *PRODH*, raising some question about the validity of the boundaries of the critical region (Weksberg et al. 2007). Third, several additional studies failed to find association of *PRODH* variants and Sz. For example, in a set of 166 Chinese parent–child trios from East China, Fan et al. (2003) found no association using only the same markers as Liu et al. (2002a). There are several possible explanations for this negative result: (i) the few markers tested did not capture the *PRODH* risk alleles in this population, (ii) the sample size is small and underpowered to detect the risk and (iii) variants at the *PRODH* locus confer no risk for Sz in this population. Unfortunately, without more genotyping on a larger sample, it is not possible to distinguish between these alternatives. In a more extensive study, Williams and colleagues genotyped a large northern European sample (677 Sz and 679 controls) plus 55 Bulgarian early onset parent–child trios and found no evidence for association with the *PRODH* SNPs

utilized by Liu et al. (2002a) and Williams et al. (2003a). To extend this analysis, Williams et al. (2003b) then searched for additional *PRODH* sequence variants by sequencing all *PRODH* exons and flanking intronic splice sites in 14 unrelated Sz probands, identifying 9 variants (8 exonic). These variants were then genotyped in pools of 368 cases and 368 controls with no one showing evidence of even suggestive association (observed *P* values were >0.1). The authors concluded "*PRODH* is not involved in the etiology of Sz". This approach would have a strong chance of identifying risk variants in the coding sequence but would miss risk variants in noncoding sequences (promoters, distant regulatory elements) of the type that experience with recent successful genomewide association studies suggest are at least as common as coding variants.(Zeggini et al. 2008).

In an alternative approach, Jacquet et al. (2002) have performed a mutation survey of 23 genes in the 22q11DS critical region in 63 unrelated Sz probands. In this relatively small number of individuals, they found two families co-segregating putative inactivating *PRODH* mutations, hyperprolinemia and Sz. These results strongly support involvement of *PRODH* in Sz. Subsequent studies of neurologically abnormal children by this group, identified a total of eight unrelated HPI probands with a neurologic phenotype characterized by early severe developmental delay, autistic features and seizures associated with hyperprolinemia and biallelic *PRODH* mutations (Afenjar et al. 2007). These results suggest that severe reduction of POX activity caused by inactivating *PRODH* mutations has the potential for causing substantial neurological abnormalities.

To provide the functional data necessary for interpretation of the consequences of *PRODH* missense mutations, Bender et al. (2005) expressed 16 different *PRODH* alleles with single missense mutations and several with multiple missense mutations. They found five missense mutations (P406L, L441P, R453C, T466M and Q521E) that result in severe reduction of POX activity (<30% of control activity) including one (T466M) that regained activity in the presence of high FAD. They also identified four missense mutations (R185Q, L289M, A455S, A472T) with minimal effect on activity (>70% of control), six (Q19P, A167V, R185W, D426N, V427M and R431H) with moderate effect on activity (30–70% of control) and one (Q521R) with increased POX activity (120% of control). Three of four alleles associated with or found in individuals with Sz were in the group with severe reduction in function.

In a provocative recent study likely to be a harbinger of future work, Zinkstok et al. (2008) used structural magnetic resonance imaging to look for correlation of genetic variation in *COMT* and *PRODH* with regional differences in gray and white matter density of the brains of 51 individuals with Sz. Interestingly, they identified *PRODH* variants that were associated with reductions in frontal lobe white matter density as well as evidence for interaction of variants in *PRODH* and *COMT* on these parameters.

Finally, in an important study, Raux et al. (2007) evaluated the consequences of hyperprolinemia and variation at the *PRODH* and *COMT* loci on cognitive and neuropsychiatric function. They collected a series of eight HPI patients and 92 adolescent or adult 22q11DS patients of which 33 (36%) had psychosis. In all they measured IQ, fasting plasma proline and *PRODH* and *COMT* genotypes. The HPI patients were ascertained in genetics clinics, ranged in age from 2–14 years and had an apparently similar phenotype of mental retardation (5/8), autistic features (4/8) and seizures (6/8). Their plasma prolines ranged from 400 to 2,200 μM with all averaging >500 μM (normal 51–271 μM). It is not clear if any of these patients are the same as previously published by this group (Jacquet et al. 2002, 2003). The authors concluded that HPI is far from a benign condition and can be characterized by profound neurological dysfunction. How this reconciles with previous views of HPI as a largely benign condition was not considered by the authors. Because these children were identified in genetics clinics, it is possible that ascertainment bias explains the association of hyperprolinemia and CNS dysfunction. However, the relative homogeneity of the phenotypic features of these patients makes this possibility less likely. Conversely, because HPI previously was a diagnosis of exclusion without enzymatic or molecular confirmation and because heterozygosity for a *PRODH* allele can cause hyperprolinemia (e.g. in 22q11DS), it is possible that many individuals previously identified as HPI patients were actually clinically asymptomatic heterozygotes. Family studies and prospective evaluation of patients identified based on hyperprolinemia will be required to sort out these possibilities.

In the second part of their study, Raux et al. (2007) used multiple regression analysis to determine the influence of plasma proline, psychosis and *COMT* genotype (the V158M functional polymorphism) on IQ in the 22q11DS patients. They observed an inverse correlation between plasma proline levels and IQ. Moreover, in the hyperprolinemic subset of the 22q11DS patients, they found that those with psychosis were more likely to carry the low activity *COMT* allele (Met158) (12/33 or 36%) than those without psychosis (10/59 or 17%) suggesting the *COMT*-Met158 genotype confers a twofold increased risk for psychosis in individuals with 22q11DS (odds ratio, OR = 2.8, 95% confidence interval = 1.04–7.4). These results need confirmation but are consistent with those in the Prodh$^{-/-}$ mouse (Paterlini et al. 2005).

## Summary and perspectives

Considerable evidence derived from studies of animal models, rare inborn errors and association studies with common *PRODH* variants in multiple populations strongly supports a role for hyperprolinemia and/or *PRODH* variants causing POX deficiency as risk factors for Sz. On balance, the evidence is compelling but not yet conclusive. Additional work is required to either confirm or refute these ideas. For example, it would be valuable to perform a fine mapping study across the entire 3 Mb 22q11DS region at high SNP density (1/kb) in a large sample of cases and controls (Li et al. 2008; Williams et al. 2006). A comprehensive survey of this type would have high likelihood of success in identifying the sources of risk that increases the incidence of Sz 25-fold in individuals with 22q11DS.

Even if we accept the evidence implicating *PRODH* variants, many questions remain to be answered. Is this effect a consequence of proline accumulation perhaps related to the proposed role of proline as an inhibitory neurotransmitter, or is it a direct consequence of deficient activity of POX? The latter could have deleterious effects in many ways, including but not limited to: (i) reduction of glutamate production from proline, perhaps in some critical subset of glutamatergic synapses; (ii) interruption of the proline/P5C redox cycle in cells critical for brain development or function; or (iii) impairment in POX-mediated apoptosis which could play a role in some critical aspect of CNS development (Hu et al. 2007; Liu et al. 2006). These possibilities are speculative but derive from increased understanding of aspects of proline metabolism as described in other articles of this compendium. The first possibility (reduced glutamate production) is consistent with the modest but statistically significant reduction of glutamate observed in the brains of Prodh$^{-/-}$ mice (Gogos et al. 1999; Paterlini et al. 2005). Work in these same animals and subsequent human studies emphasizes the importance of considering other variables such as the *COMT* genotype and overall state of the dopaminergic system (Diaz-Asper et al. 2008; Paterlini et al. 2005; Raux et al. 2007; Sei et al. 2007). Exciting new functional imaging studies should be utilized and performed in conjunction with genetic information (Goldman et al. 2008). From these considerations, it is obvious that much work remains to be done especially as to the physiologic functions of proline and *PRODH* in the brain during development and in normal homeostasis. The Prodh$^{-/-}$ mouse is an excellent resource that should continue to be exploited (Paterlini et al. 2005). For example, it should be possible to build derivative models adding in risk alleles at other loci (e.g. *Comt*) so that risk variants could be tested alone and in combinations. Similarly, more and better phenotypic, biochemical and molecular information needs to be obtained in patients with either HPI or HPII. Finally, there is more to be learned from the collection of 22q11DS patients in terms of who develops Sz and why. The answers are sure to be interesting and to provide greater insight into the mystery that is Sz.

The results to date also suggest that we are entering a new era when patients newly diagnosed with a neuropsychiatric disorder should be evaluated with metabolic and molecular testing. For example, in our opinion all newly diagnosed Sz patients should be evaluated with a fasting plasma amino acid determination and a molecular cytogenetic test for 22q11DS deletions as well as genotyping for *COMT, PRODH* and other candidate risk genes for Sz.

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