

# A Case for Cannabidiol in Wolf–Hirschhorn Syndrome Seizure Management

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Complex, and sometimes intractable, seizures affect the quality of life and cognitive development of over 90% of individuals with Wolf–Hirschhorn syndrome (WHS). Fine resolution genotype–phenotype mapping of the WHS locus recently identified a candidate gene whose probable function has led to insights into a mechanism connecting WHS seizures with those of Dravet syndrome, a distinct condition caused by mutations in *SCN1A* and *SCN1B*. In addition to this possible molecular mechanistic connection, these disorders' seizures share a strikingly similar constellation of features, including clinical presentation, seizure types, early age of onset, EEG pattern, and responses to specific anti-epileptic drugs. Based in part on these similarities, we suggest that a highly successful Phase III clinical trial of a formulation of cannabidiol for Dravet syndrome seizures may be directly translatable into possible benefits for WHS individuals with challenging seizure patterns. © 2016 Wiley Periodicals, Inc.

**Key words:** cannabidiol; seizures; Wolf–Hirschhorn syndrome; Dravet syndrome

## COMMENTARY

Wolf–Hirschhorn syndrome (WHS; OMIM #194190) is a contiguous gene deletion disorder occurring in 1:20,000–1:50,000 births [Maas et al., 2008; Battaglia et al., 2015] first described by Hirschhorn and Cooper in 1961, and clearly defined as a syndrome with publications by Wolf et al. and Hirschhorn et al. in 1965 [Hirschhorn, 2008]. Long known to be due to variable deletions of the short arm of chromosome 4 (4p-), WHS is characterized by a specific pattern of craniofacial features, prenatal and postnatal growth delay, intellectual disability (ID) and seizures [Hirschhorn, 2008; Maas et al., 2008; South et al., 2008; Battaglia et al., 2015]. Seizures occur in over 90% of individuals with onset typically within the first 3 years of life. Most individuals with WHS have a complex pattern of seizure types, with frank status epilepticus events occurring in up to 50% of individuals with WHS [Battaglia et al., 2009, 2015]. At least 15% of parents surveyed report an intractable seizure pattern in their affected children [Markham et al., 2016]. Seizures therefore represent a significant negative factor for quality of life and outcome in WHS.

The availability of chromosomal microarray analysis (CMA) has lead to evolution of our understanding of the genomic variation

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within WHS and its correlation with phenotype [Maas et al., 2008; South et al., 2008; Battaglia et al., 2015]. Recently, we described a novel candidate region for the seizures associated with WHS [Ho et al., 2016]. The most plausible candidate gene in the region, *PIGG*, encodes an enzyme responsible for one step in a biosynthetic pathway that assembles and attaches a phosphatidylinositol glycan (GPI) anchor to over 150 separate proteins in order to direct them to the outer leaflet of the plasma membrane where they carry out various signaling and extracellular functions [Kinoshita, 2014]. Deficiencies in GPI anchor synthesis, including those caused by variants in *PIGG*, underlie congenital disorders of glycosylation, which are associated with infantile encephalopathy, ID, and/or seizures [Makrythanasis et al., 2016].

The identification of *PIGG* as potential critical contributor to the seizures in WHS has opened the door to potential therapeutic strategies in these patients by virtue of our observation that the GPI pathway constitutes a possible mechanistic link with the complex seizures characteristic of another genetic condition, Dravet Syndrome [Battaglia and Carey, 2005; Battaglia et al., 2009; Chopra and Isom, 2014]. Nakano et al. [2010] demonstrated in zebrafish that lack or knock-down of functional members of the GPI biosynthetic pathway results in the failure of the *Scn1bb* sodium channel to localize to the plasma membrane. Zebrafish *scn1bb* is the homolog of human *SCN1B*, mutations in which, or in its human

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ortholog, *SCN1A*, are linked etiologically to infantile encephalopathies including Dravet syndrome [Chopra and Isom, 2014].

Beyond this potential mechanistic link, there are significant similarities shared between WHS and Dravet syndrome. Seizures in both have a complex pattern, can be prolonged, are often brought on by febrile episodes, and are often intractable to pharmacotherapies, leading to cognitive, motor, and behavioral impairment [Battaglia and Carey, 2005; Chopra and Isom, 2014]. Some patients with a milder WHS-related dysmorphology have been first suspected to have Dravet syndrome, and only correctly diagnosed by CMA after negative sequence analysis of *SCN1A* [Bayindir et al., 2013; Zollino et al., 2014]. The EEG pattern in WHS is distinctively similar to that observed in Dravet syndrome [Battaglia and Carey, 2005; Battaglia et al., 2009]. They also show similar response patterns to specific anti-epileptic drug (AED) regimens, with carbamazepine known to exacerbate seizures, while in contradistinction, bromide and valproate show some efficacy in both individuals with WHS as well as individuals with Dravet syndrome [Brunklau et al., 2012; Itakura et al., 2016; Markham et al., 2016; Shi et al., 2016].

Earlier this year, GW Pharma announced positive results of a two arm pivotal Phase 3 study of its investigational cannabidiol (CBD) medication, Epidiolex<sup>®</sup> in 120 refractory patients with Dravet syndrome, with a median reduction in monthly seizure episodes of 39% compared to only 13% on placebo ( $P = 0.01$ ) over the 14-week treatment period compared with the 4-week baseline observation period [GWPharma—GW Pharmaceuticals Announces Positive Phase 3 Pivotal Study Results for Epidiolex<sup>®</sup> [cannabidiol] 2016]. The median baseline convulsive seizure frequency per month was 13. This drug has both Orphan Drug Designation and Fast Track Designation from the U.S. Food and Drug Administration (FDA) in the treatment of Dravet syndrome, and more recently comparable results were reported in the clinically similar condition, Lennox–Gastaut syndrome.

Based upon this marked clinical similarity and the potential mechanistic link, Markham et al. specifically inquired about use of cannabinoids in any form in an online survey of parents from the 4p-Support Group concerning the response of their child with WHS to specific seizure treatments. Roughly, 5% (5/95) indicated use of such alternative agents; however, it is likely that this represents under-reporting as the survey was not anonymous and such agents are not legal in many jurisdictions still today. Of those who reported use of cannabinoids, 80% noted a reduction in seizure frequency of over 50%, as well as related benefits in terms of reduced side effects from lowered AED therapy dosage [Markham et al., 2016].

Detyniecki and Hirsch [2016] opined in their editorial on a recent, apparently positive open-label interventional trial with CBD [Devinsky et al., 2016], that there is potential for a large placebo effect with highly motivated parents in such anecdotal reports and open-label uncontrolled studies. Filloux [2015] has commented thoughtfully on the need for “real science” in approaching the issue of cannabinoid use in epilepsy in general. While acknowledging these challenges, we nevertheless strongly believe that the noted mechanistic links and clinical similarities between WHS and Dravet syndrome, and the sound studies supporting CBD use in the latter condition, indicate that serious

consideration should be given to CBD use in WHS individuals who are not achieving good seizure control with minimized AED side effects and optimal quality of life. Ideally, this would be through a separate arm of the prior Phase III studies for label extension or in new IND submission studies by other drug manufacturers. In the absence of this option, geneticists caring for such patients should seriously consider referring their patients with WHS to centers engaged in an ongoing open-label trial. The strength of the former approach is the increased likelihood that, by deliberately selecting a cohort on the basis of similar genetic etiology, the likely positive CBD response can be detected in a controlled manner, above potential placebo effect.

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