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Case report of PLXNA4 variant associated with hyper-response to phentermine/topiramate pharmacotherapy: Potential genetic basis for superior weight loss response?

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ABSTRACT

Background: Once thought to be primarily a result of lifestyle, it is now known that obesity has significant genetic components. Dozens of genes have been linked to obesity, and office-based genetic testing for obesity-associated genes is now readily available. As both pharmacotherapy and genetic testing for obesity become more accessible, pharmacogenetic personalization is becoming a reality. In this case report, a patient with a PLXNA4 polymorphism had a superior weight loss response to phentermine/topiramate therapy than has previously been reported in the literature. Thus, variants in PLXNA4 may provide a genetic basis for this patient's superior response to weight loss pharmacotherapy and cardiovascular risk factor reduction.

Methods: In this case study, office-based genetic testing was utilized to identify the presence of variants in nearly 80 genes that have been linked to obesity in a patient who had hyper-responsive weight loss results on phentermine/topiramate pharmacotherapy.

Results: A variant of the PLXNA4 gene, which has known pathogenic variants linked to genetic obesity syndromes, was identified in this patient who had a superior weight loss response to phentermine/topiramate pharmacotherapy.

Conclusion: Due to overlapping molecular pathways, it is possible that PLXNA4 variants convey a superior weight-loss response and therefore superior cardiovascular risk factor reduction phentermine/topiramate therapy. Further studies are needed to examine the relationship between PLXNA4 variants and weight loss with phentermine/topiramate pharmacotherapy.

1. Introduction

The objective of this case report is to describe a case of hyper-response to phentermine/topiramate therapy for weight loss in the setting of a PLXNA4 variant. Phentermine is a sympathomimetic amine which primarily increases norepinephrine and dopamine receptor activity, and to a smaller degree serotonin [1,2]. Through this mechanism, food intake is reduced and energy use is increased. Topiramate is a sulfamate-substituted monosaccharide primarily used as an anti-epileptic and migraine prophylactic [1–3]. Topiramate acts as both an agonist and antagonist on multiple central and peripheral receptors; its weight-loss mechanism is not completely understood but is believed to be a result of gamma-aminobutyric acid (GABA) modulation and increased dopamine release [1–4]. In previous studies, subjects with overweight and obesity on phentermine/topiramate pharmacotherapy lost between 5 and 10% of total body weight with one year of therapy and 9.3–10.7% of total body weight with two years of therapy, concurrent with lifestyle modification [2,5,6]. While there are many pathways through which weight and homeostasis are regulated, in this case, the pathway of interest includes PLXNA4. PLXNA4 is one of several receptors involved in semaphorin signaling within the hypothalamus [7,8]. Heterozygous missense mutations in PLXNA4 have also been linked to severe, early-onset obesity [9]. To our knowledge, pharmacogenetic analysis is not currently available for phentermine and topiramate in relation to PLXNA4; however, in this case report, a patient with a PLXNA4 variant saw more than 3.5 times the amount of expected weight loss on phentermine/topiramate therapy over a 15-month period.

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2. Patient information

Our patient was a 29-year-old woman seeking medical and surgical weight loss options after unsuccessful attempts at weight loss through lifestyle modification. Patient reported being bigger than other children by age 8, followed by progressive weight gain as she grew older. This weight gain further accelerated as an adult. Medical history was significant for dyslipidemia, hypertension, obstructive sleep apnea, and prediabetes. At her initial visit, this patient was prescribed and actively taking five anti-hypertensive medications (carvedilol, amlodipine, hydrochlorothiazide, torsemide, and valsartan) in addition to atorvastatin and cholestyramine for dyslipidemia.

3. Clinical findings

At her initial appointment, this patient weighed 185.3 kg (407.7 lbs; BMI 68.1) and had a blood pressure of 132/66 mmHg on five anti-hypertensives. Physical exam demonstrated excess abdominal adiposity and large dorsocervical fat pad.

4. Timeline

5. Diagnostic assessment

Initial laboratory evaluation was significant for a total cholesterol of 182 mg/dL with LDL 129 mg/dL and triglyceride 189 mg/dL, and A1c of 5.6%. Binge Eating Severity Scale was administered with a result of 16, indicative of none-to-minimal binge eating behaviors. Workup for potential secondary causes of obesity, including hypothyroidism and excess cortisol, was normal.

6. Therapeutic intervention

At her initial visit, she was started on phentermine 37.5 mg daily and topiramate 50 mg daily for weight loss. After 19 weeks, her dose of topiramate was increased to 50 mg twice daily and her dose of phentermine was maintained. During this initial 19-week interval, the patient lost 8 kg (17.8 lbs) and decided to defer surgical management in favor of continued medical therapy, exercise, and dietary improvements. Injectable once weekly semaglutide was trialed but discontinued after only 3 weeks due to intractable nausea. Phentermine/topiramate pharmacotherapy was continued uninterrupted during this failed trial of semaglutide.

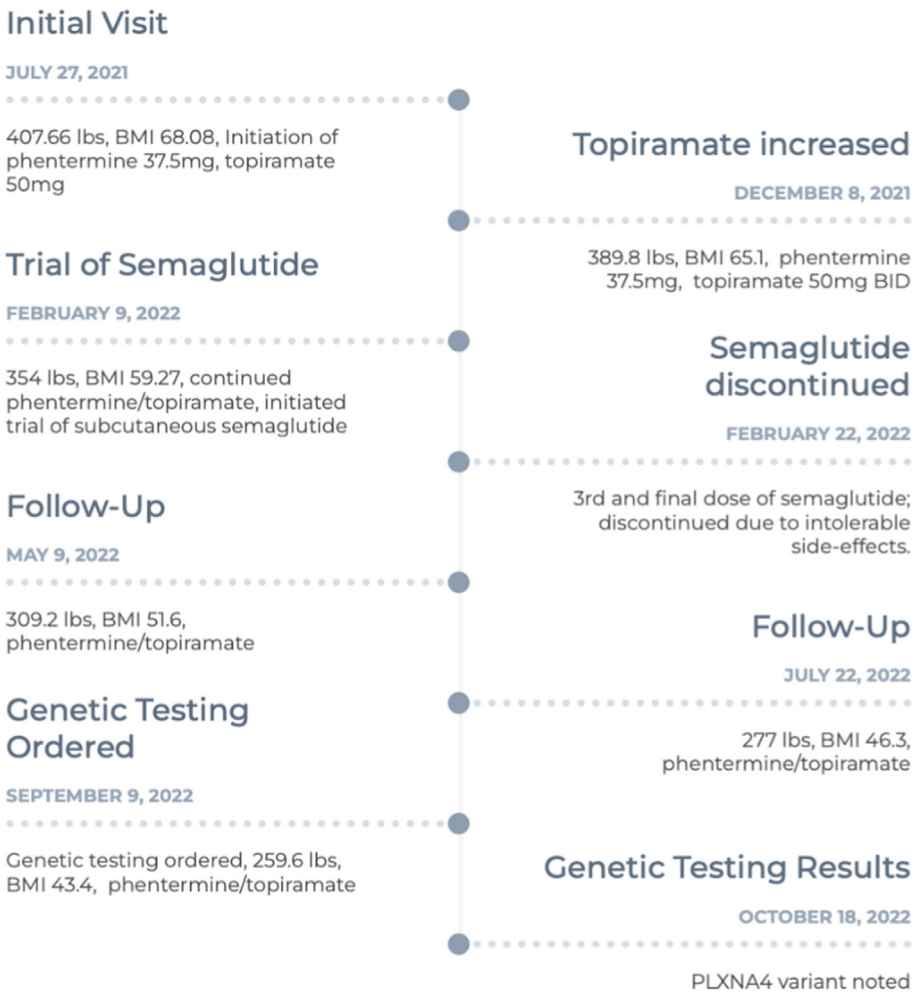

Fig. 1. Timeline of case from initial presentation to discovery of PLXNA4 variant, spanning 15 months of treatment with phentermine/topiramate therapy.

7. Follow-up and outcomes

Over the course of 58 weeks of phentermine/topiramate pharmacotherapy, the patient lost a total of 67.3 kg (148 lbs), achieving a BMI of 43.4 [Fig. 1]. This amounted to a weight loss of 36.3% (and BMI reduction of 24.7 kg/m^2) over the span of 15 months. This is at least 3.5 times more than the expected 5–10% weight loss on this regimen over the course of a year [5], which classifies this patient as a "hyper-responder" [10] to phentermine/topiramate therapy.

As a result of her significant weight loss, the patient was able to down-titrate her blood pressure medications under the supervision of her cardiologist after 7 months of phentermine/topiramate therapy (at which time she had lost 60 lbs, approximately 15% of her initial body weight). After 8 months of therapy, she discontinued use of her CPAP due to significant improvement in symptoms of OSA. Her thiazide diuretic was discontinued after 9 months of therapy and her angiotensin-receptor blocker, calcium channel blocker, and beta-blocker were discontinued by 12 months of therapy. Repeat Binge Eating Severity Scale questionnaire was administered with a result of 1, a 15-point decrease compared to her initial appointment.

Due to her unprecedented weight loss, history of pediatric obesity, and high suspicion of genetic contribution to weight gain, genetic testing was performed and a PLXNA4 variant was noted. No link between PLXNA4 and a superior response to phentermine/topiramate therapy has previously been reported in the literature.

8. Discussion

In this case study, a phentermine/topiramate hyper-responder was found to have a PLXNA4 variant on genetic testing. With over 35% body weight loss, this patient saw significant improvements in her cardiovascular risk factors and was able to defer surgical management. The identified PLXNA4 variant provides a potential genetic basis for her hyper-responder status, and, therefore, her improved cardiovascular risk factors.

The association between obesity and cardiovascular disease is well-established [11,12]. Accordingly, weight loss in people with obesity has been linked to improvement in cardiovascular risk factors. In one study, individuals with obesity who lost >5% of their weight had decreased incidence of type 2 diabetes, hypertension, and hyperlipidemia at 2 years compared to those who maintained their weight [13]. This relationship was shown to be dose-dependent, as individuals with obesity who lost >15% of their body weight had a significantly lower incidence of type 2 diabetes, hypertension, and hyperlipidemia compared to those who lost <7% of their initial weight [13]. This case study is an excellent example of cardiovascular risk factor reduction with weight loss, evidenced by this patient's profound improvement in blood pressure control, obstructive sleep apnea, and dyslipidemia.

Obesity, particularly severe obesity, has a strong genetic association. Just as combining pharmacotherapies can improve clinical outcomes, incorporating genetics into clinical management decisions has the potential to improve clinical outcomes by taking into consideration a patient's unique genetic makeup when selecting pharmacotherapy. Genetic testing has expanded radically in the last decade, with improvements in both the breadth and availability of testing. To date, dozens of gene variants have been linked to obesity and, therefore, exacerbation of cardiovascular risk factors. While an in-depth review of best practices for genetic testing is beyond the scope of this paper, current guidelines addressing genetic testing for cardiovascular disease emphasize the importance of testing only patients with a strong clinical suspicion of a disease, providing adequate pre- and post-test counseling, and changing clinical management as appropriate based on results [14].

Pharmacotherapy plays a multifaceted role in this case. Like many of the patients we treat, this patient presented taking multiple prescription medications, including carvedilol for blood pressure control. While carvedilol is thought to be less obesogenic than other beta-blockers, this medication class has been linked to mild weight gain [15]. Given this patient's history of childhood obesity and current severe obesity, it is unlikely that this medication played a role in her initial weight gain. However, it is possible that cessation of this medication over the course of her weight loss may have contributed to a small amount of additional weight loss. While prescription medications may not have played a large role in this patient's severe obesity, several classes of prescription medications have been linked to weight gain or hindered weight loss—most notably antipsychotics, antidepressants, and anti-epileptics [16]. For this reason, medication reconciliation is a crucial part of any medical weight management office visit.

Perhaps the more significant aspect of pharmacotherapy relevant to this case involves the mechanisms of phentermine and topiramate in relation to weight loss. Phentermine is chemically related to amphetamines and works by increasing norepinephrine, dopamine, and serotonin levels within the CNS, which causes decreased appetite and weight loss [1,4,17–20]. Topiramate-associated weight loss is thought to be a secondary effect of its neuro-stabilizing properties [1]. It is proposed that by modulating voltage-gated sodium and calcium channels, AMPA/KA receptors, and GABA receptor currents, as well as by inhibition of carbonic anhydrase 8, topiramate decreases food cravings and increases levels of catabolic hormones while potentially increasing endogenous GLP1 production [1,4,17,18,21]. When combined, phentermine and topiramate target the hypothalamus and brainstem to provide effective weight loss therapy and produced an average weight loss of 5–10% [1,2,5].

To our knowledge, there are no studies in the literature examining the relationship between the mechanisms of phentermine/topiramate and the PLXNA4 gene. However, the PLXNA4 product (plexin A4) is known to function with semaphorin 6A and itself is localized in the hypothalamus [8,22]. Semaphorins function as signaling proteins necessary for development and maintenance of organs and tissues by regulating morphology and motility [7,8]. They are in turn regulated by plexin A4 to prevent abnormal mossy fiber projection in the hippocampus [7]. When down-regulated, semaphoring 6A may disrupt macrophage-neuron crosstalk in brown adipose tissue formed due to ineffective homeostatic energy expenditure [7,22,23]. Through semaphorin receptor regulation, PLXNA4 is proposed to alter energy expenditure within the body [22]. This is comparable to the weight loss mechanisms of phentermine and topiramate. The pathways through which weight regulation occurs differs between the PLXNA4 gene pathway and the pharmacotherapies in question; however, given the superior weight loss on phentermine/topiramate in this patient with a PLXNA4 abnormality, it is plausible that there exists a synergistic intersection between the mechanisms, resulting in a superior weight loss response.

This case adds to the list of genes known to be associated with a variable weight loss response [2,5,24] and provides a potential genetic explanation for this patient's "hyper-responder" [10] status to phentermine/topiramate. As availability of genetic testing expands, tailoring of medication based on a patient's genetics will continue to become more important to achieve the maximal effect of pharmacotherapy. Based on this case study, it is possible that PLXNA4 gene variants may convey a superior weight loss response to phentermine/topiramate in patients with obesity, therefore adding to the field of pharmacogenetic personalization in weight management. This association between PLXNA4 abnormalities and hyper-response to anti-obesity medications should be further evaluated in prospective studies.

9. Patient perspective

As a result of her significant weight loss, this patient saw significant improvement in her cardiometabolic risk factors; under medical supervision, she was able to discontinue four out of her five previously prescribed blood pressure medications as well as her atorvastatin and cholestyramine. In addition, she was able to discontinue the use of her nightly CPAP machine due to significant improvement in her obstructive sleep apnea. Her high satisfaction with medical therapy resulted in her choosing to defer bariatric surgery in favor of continued medical and lifestyle intervention.

10. Informed consent

The patient in question provided informed consent to be included in this case report.

Author contribution

MP wrote the original draft of this manuscript. MFD reviewed and expanded upon original draft and assisted with editing. JR conceptualized this submission and assisted with editing the manuscript.

Ethical review

This submission represents original work and has appropriately cited reference material. Authors received consent from the patient prior to initiation of this case report.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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