

ORIGINAL ARTICLE

Serine and Lipid Metabolism in Macular Disease and Peripheral Neuropathy

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ABSTRACT

BACKGROUND

Identifying mechanisms of diseases with complex inheritance patterns, such as macular telangiectasia type 2, is challenging. A link between macular telangiectasia type 2 and altered serine metabolism has been established previously.

METHODS

Through exome sequence analysis of a patient with macular telangiectasia type 2 and his family members, we identified a variant in *SPTLC1* encoding a subunit of serine palmitoyltransferase (SPT). Because mutations affecting SPT are known to cause hereditary sensory and autonomic neuropathy type 1 (HSAN1), we examined 10 additional persons with HSAN1 for ophthalmologic disease. We assayed serum amino acid and sphingoid base levels, including levels of deoxysphingolipids, in patients who had macular telangiectasia type 2 but did not have HSAN1 or pathogenic variants affecting SPT. We characterized mice with low serine levels and tested the effects of deoxysphingolipids on human retinal organoids.

RESULTS

Two variants known to cause HSAN1 were identified as causal for macular telangiectasia type 2: of 11 patients with HSAN1, 9 also had macular telangiectasia type 2. Circulating deoxysphingolipid levels were 84.2% higher among 125 patients with macular telangiectasia type 2 who did not have pathogenic variants affecting SPT than among 94 unaffected controls. Deoxysphingolipid levels were negatively correlated with serine levels, which were 20.6% lower than among controls. Reduction of serine levels in mice led to increases in levels of retinal deoxysphingolipids and compromised visual function. Deoxysphingolipids caused photoreceptor-cell death in retinal organoids, but not in the presence of regulators of lipid metabolism.

CONCLUSIONS

Elevated levels of atypical deoxysphingolipids, caused by variant *SPTLC1* or *SPTLC2* or by low serine levels, were risk factors for macular telangiectasia type 2, as well as for peripheral neuropathy. (Funded by the Lowy Medical Research Institute and others.)

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UNDERSTANDING THE PATHOPHYSIOLOGY of diseases with complex genetic inheritance patterns is challenging. Macular telangiectasia type 2, which has a prevalence of 0.0045% to 0.06%, is a rare macular disease that leads to loss of central vision, with the onset of symptoms occurring in the fifth or sixth decade of life.¹⁻⁴ The condition has a strong genetic component, as evidenced by extended families having multiple affected family members.⁵ However, the inheritance pattern is not clear because of the variable penetrance and expressivity of the disease.^{6,7} Recent insights into macular telangiectasia type 2 have come from genomewide association and metabolomic studies, which have suggested that it is associated with low serine levels in blood.⁸ Serine is a substrate in numerous metabolic pathways, including protein, nucleotide, and lipid synthesis. Whether and how low levels of serine affect macular health is unknown.

Serine palmitoyltransferase (SPT) condenses serine and palmitoyl-CoA and is the rate-limiting enzyme in sphingolipid synthesis.⁹ Variants in the genes *SPTLC1* and *SPTLC2*, encoding two SPT subunits, result in the increased synthesis of atypical deoxysphingolipids and are causative for the rare disorder hereditary sensory and autonomic neuropathy type 1 (HSAN1).¹⁰⁻¹² Deoxysphingolipids are toxic to multiple cell types, especially neurons.^{10,13-17} In vitro studies have shown that deoxysphingolipids can also accumulate in the absence of mutations in *SPTLC1* or *SPTLC2* when levels of serine are low.¹⁸ In this study, we investigated the role of deoxysphingolipids in macular telangiectasia type 2 and examined how a metabolic defect might lead to disease in both the eye and the peripheral nervous system.

METHODS

STUDY PARTICIPANTS AND GENETIC ANALYSES

We enrolled patients with macular telangiectasia type 2, HSAN1, or both conditions, as well as available family members and unaffected controls; all participants provided written informed consent, and the study was approved by local institutional review boards. Clinical diagnoses were confirmed by experienced retina specialists at the Moorfields Eye Hospital Reading Centre who were not aware of previous diagnoses. Genomic DNA from patients with macular telangi-

ectasia type 2 and their family members was analyzed by exome sequencing. Exome sequence was captured with SeqCap EZ Exome, version 3. Raw sequence data were quality filtered with CASAVA (Illumina) and aligned to the Human Reference Genome, build hg19. All potentially disease-associated variants that were detected were confirmed by Sanger sequencing.

CLINICAL EXAMINATIONS

All participants underwent dilated retinal examination and standard ophthalmic imaging, conducted with the use of a Heidelberg Spectralis confocal imaging system. Dual-wavelength autofluorescence macular pigment imaging and fluorescence lifetime imaging ophthalmoscopy (FLIO) were performed with prototype instruments provided by Heidelberg Engineering.¹⁹

STATISTICAL ANALYSIS

Linear mixed models controlling for covariates with a significant effect on metabolite levels in plasma were used to assess differences in these levels between unaffected persons and persons with macular telangiectasia type 2. For all experiments, P values from tests performed on the same data set were corrected for multiple testing by the Benjamini–Hochberg procedure. The regression coefficient *b* represents the magnitude of the effect. (Additional details of the statistical analysis, as well as details of the experiments conducted in mice and cell culture, are provided in Supplementary Appendix 1, available with the full text of this article at NEJM.org.)

RESULTS

HSAN1 AND SUSCEPTIBILITY TO MACULAR TELANGIECTASIA TYPE 2

A 21-year-old man (Family Member III-3 [Family 1] in Fig. 1 and Table 1) presented with bull's-eye maculopathy in both eyes. Clinical examination revealed findings diagnostic for macular telangiectasia type 2, including parafoveal telangiectatic retinal vessels, “right angle” venules, retinal opacification, pigment clumping, low levels of macular carotenoid pigment, late and mild leakage on fluorescein angiography, blue light–reflectance abnormalities, and intraretinal cysts and ellipsoid zone defects on optical coherence tomography (OCT). His parents and both siblings

were then examined, which led to a diagnosis of macular telangiectasia type 2 in the father (II-2). One sister (III-2) was described as “possibly affected” because of reduced macular pigment and subtle parafoveal leakage as revealed by late-phase fluorescein angiography. The other sister (III-1) was not affected. The proband and his father and possibly affected sister reported having a familial peripheral neuropathy that had been diagnosed as Charcot–Marie–Tooth disease.

Exome sequencing revealed that these family members had the p.Cys133Tyr mutation in *SPTLC1* (variant NM_006415.3 [SPTLC1]: c.398G→A; genomic location, 9:92080045 [GRCh38]; ClinVar accession number, VCV000004800.1),²⁰ which is diagnostic of the rare disorder hereditary sensory and autonomic neuropathy type 1A (HSAN1A).²⁰ The variant is pathogenic according to American College of Medical Genetics criteria for causality²¹ and cosegregated with both macular telangiectasia type 2 and HSAN1A in this family (Fig. 1B).

To determine whether HSAN1-associated mutations are causal for macular telangiectasia type 2, we examined 10 consecutive patients with HSAN1 (including members of two additional affected families) who had no known relationship to the index family (Table 1, and Fig. S1 in Supplementary Appendix 1). Six patients carried the p.Cys133Tyr mutation, two carried the p.Cys133Trp mutation in *SPTLC1*, and two carried the p.Ser384Phe mutation in *SPTLC2*, a variant previously shown to result in increased deoxysphingolipid levels and to cause HSAN1C, a disease closely related to HSAN1A (Table 1).²² Macular telangiectasia type 2 is an orphan disease, affecting approximately 1 in 5000 persons.^{3,4} We observed macular telangiectasia type 2 in 9 of the 13 patients with HSAN1 we examined ($P=2.2\times 10^{-16}$ by one-sided binomial test). Of the remaining 4 patients with HSAN1, 2 had abnormal macular features (III-2 in Family 1) or macular telangiectasia type 2–associated changes (III-2 in Family 1 and III-2 in Family 2). All 4 patients were younger than 50 years of age and were too young for a definitive diagnosis; they were also taking serine supplements, which may delay disease onset. The macular telangiectasia type 2 phenotype observed in the patients with HSAN1 was typical of that observed in the patients without HSAN1. We further characterized 6 patients with HSAN1 (including those graded as unaffected or possibly

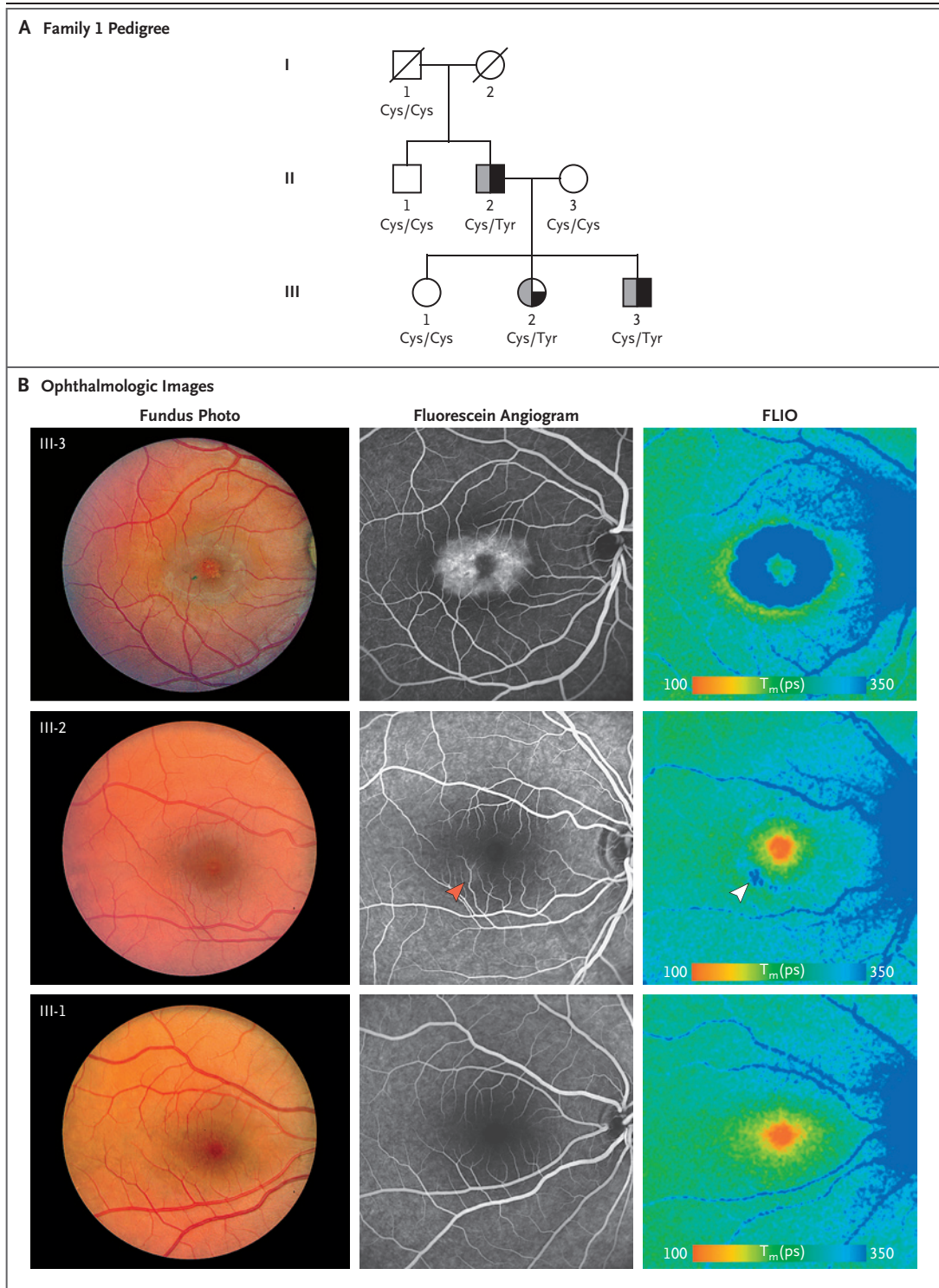
affected) with the use of FLIO. Each patient had changes characteristic of macular telangiectasia type 2 (parafoveal shifts to longer fluorescence lifetimes),¹⁹ whereas family members without HSAN1A-associated mutations had normal FLIO images (Fig. 1B, and Fig. S1B in Supplementary Appendix 1).

Family Members I-2 and II-1 in Family 3, who were carrying the p.Ser384Phe mutation in *SPTLC2* (causing HSAN1C²²), also had a diagnosis of macular telangiectasia type 2 (Fig. S1 in Supplementary Appendix 1). The two patients with HSAN1A who had the *SPTLC1* p.Cys133Trp variant (Patient 2 and Patient 3), which is also associated with high deoxysphingolipid levels,¹⁸ were designated as not affected with macular telangiectasia type 2. Both patients were younger than 50 years of age.

DEOXYSPHINGOLIPID LEVELS IN PATIENTS WITH MACULAR TELANGIECTASIA TYPE 2

Although the majority of patients with macular telangiectasia type 2 do not have a pathogenic variant affecting either subunit of SPT, they have lower levels of serine in serum than do unaffected controls.⁸ Under low-serine conditions, alanine incorporation by SPT is increased, which results in the generation of deoxysphingolipids that lack the hydroxyl moiety critical for synthesis and degradation of more complex sphingolipids (Fig. 2A).^{9,23} To determine whether deoxysphingolipid levels are elevated in patients with macular telangiectasia type 2, we assayed amino acids and total hydrolyzed sphingoid bases in serum specimens from 125 nonconsanguineous patients with the condition and 94 unaffected controls (Table S1 in Supplementary Appendix 1). We had previously sequenced the exomes of these patients and found no pathogenic variants in *SPTLC1* or *SPTLC2*.

We used linear mixed models to assess whether there were differences in metabolite levels between patients with macular telangiectasia type 2 and unaffected controls. The effect of available covariates (ethnic group, sex at birth, age, collection site, and diabetes status) was estimated, and only significant covariates were included in the final model. We detected no significant differences in levels of sphinganine ($b=0.043$, $P=0.476$) but found that levels of serum deoxysphinganine were, on average, 84.2%



higher in the cohort with macular telangiectasia type 2 ($b=0.611$, $P=1.04 \times 10^{-10}$), indicating that levels of these toxic lipids are elevated in the broader (non-HSAN1) population of patients with the condition (Fig. 2B and 2C; the data set for

the graphs shown in Fig. 2 are provided in Supplementary Appendix 2, available at NEJM.org). To address whether deoxysphingolipid levels correlated with disease severity, we analyzed the relationship between deoxysphingolipid levels

Figure 1 (facing page). Macular Telangiectasia Type 2 in Patients with Hereditary Sensory and Autonomic Neuropathy Type 1A (HSAN1A) and the *SPTLC1* p.Cys133Tyr Variant.

Panel A shows a pedigree of Family 1. Squares indicate male family members, and circles female family members; a slash through a symbol indicates that the family member is deceased. A half-solid symbol indicates macular telangiectasia type 2, and a half-gray symbol indicates HSAN1A. The quarter-solid symbol representing Family Member III-2 indicates possibly affected status. The amino acid status of *SPTLC1* at position 133, as predicted on the basis of the genetic variants, is shown. Panel B shows ophthalmologic images of Family Members III-3 (affected), III-2 (possibly affected), and III-1 (unaffected), highlighting features of macular telangiectasia type 2, including temporal right-angle vessels, parafoveal opacification, and pigment clumping. Late-fluorescein angiographic images show strong parafoveal hyperfluorescence in III-3, subtle inferotemporal hyperfluorescence in III-2 (red arrowhead), and no hyperfluorescence in the unaffected family member, III-1. Fluorescence lifetime imaging ophthalmoscopy (FLIO) images of Family Member III-3 show a characteristic parafoveal blue ring of long FLIO lifetimes and redistribution of the foveal macular pigment in an orange ring of short FLIO lifetimes around the macular telangiectasia type 2 area. Family Member III-2 has a less intense blue parafoveal ring that is most pronounced at the same site where fluorescein staining was observed (white arrowhead). The unaffected sister (III-1) has a normal FLIO with normal macular pigment (orange spot centered on the fovea) and no parafoveal blue ring. T_m (ps) denotes mean fluorescence lifetime in picoseconds.

and a quantifiable anatomical abnormality, loss of the ellipsoid zone (representing a break in the OCT reflectance pattern). The extent of loss is known to correlate with function as assessed by microperimetry²⁴⁻²⁷ and hence can be used as a measure of disease progression. We found a positive relationship between ellipsoid-zone loss and deoxysphinganine levels in the 125 patients with macular telangiectasia type 2 ($b=0.148$; 95% confidence interval, 0.004 to 0.299). (Additional details of these analyses are provided in Tables S2 through S6, S9, and S10 in Supplementary Appendix 1.)

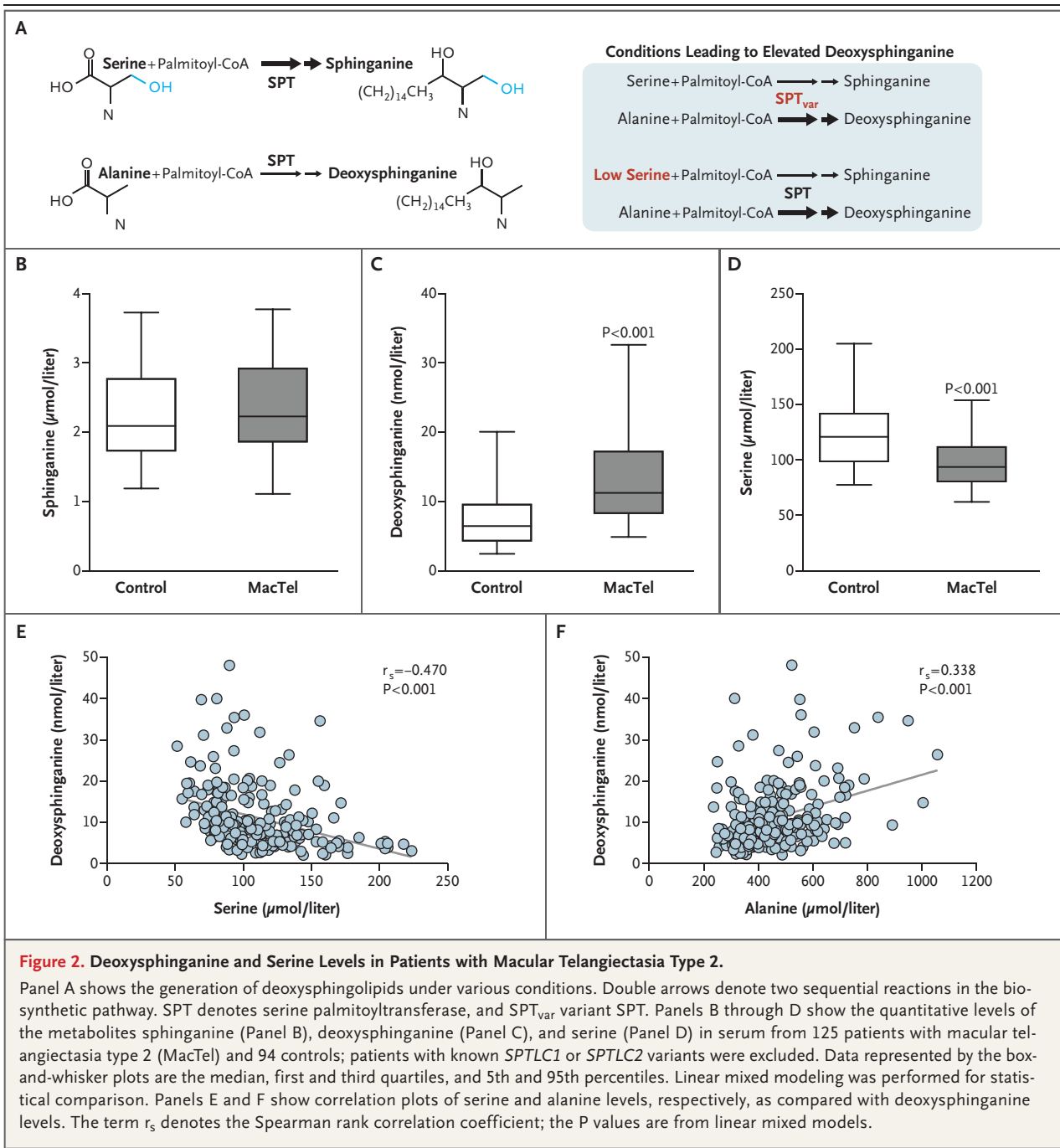
Elevated deoxysphinganine levels have been reported in patients with type 2 diabetes,^{13,28} and patients with macular telangiectasia type 2 have a higher prevalence of type 2 diabetes than the general population.²⁹ We therefore evaluated the relationship among these two conditions and deoxysphinganine levels. We found that deoxysphinganine levels were not significantly higher in patients with macular telangiectasia type 2 who had type 2 diabetes than in those who did not have type 2 diabetes ($b=0.328$, $P=0.07$) (Table S5 in Supplementary Appendix 1). Among persons who did not have macular telangiectasia type 2, levels did not differ significantly between those who had type 2 diabetes and those who did not ($b=-0.116$, $P=0.46$). When patients with type 2 diabetes were excluded from the entire group,

Table 1. Genetic and Clinical Features of Patients with Hereditary Sensory and Autonomic Neuropathy Type 1.*

Family and Patient No.	Variant Affecting SPT	Sex	Birth Year (Age in Years)	Macular Telangiectasia Type 2 Status	FLIO	Serine Supplementation†
Family 1						
III-3	<i>SPTLC1</i> p.Cys133Tyr	M	1994 (24)	Affected	Positive	No
II-2	<i>SPTLC1</i> p.Cys133Tyr	M	1965 (53)	Affected	Positive	No
III-2	<i>SPTLC1</i> p.Cys133Tyr	F	1992 (26)	Possibly affected	Positive	No
Family 2						
III-2	<i>SPTLC1</i> p.Cys133Tyr	F	1980 (38)	Unaffected	Positive	Yes
II-2	<i>SPTLC1</i> p.Cys133Tyr	F	1951 (67)	Affected	Positive	Yes
III-3	<i>SPTLC1</i> p.Cys133Tyr	M	1953 (65)	Affected	NT	Yes
III-1	<i>SPTLC1</i> p.Cys133Tyr	M	1974 (44)	Affected	Positive	Yes
IV-1	<i>SPTLC1</i> p.Cys133Tyr	F	1972 (46)	Affected	NT	Yes
Patient 1	<i>SPTLC1</i> p.Cys133Tyr	F	1963 (55)	Affected	NT	Yes
Family 3						
II-1	<i>SPTLC2</i> p.Ser384Phe	M	1974 (44)	Affected	NT	No
I-2	<i>SPTLC2</i> p.Ser384Phe	M	1953 (65)	Affected	NT	No
Patient 2	<i>SPTLC1</i> p.Cys133Trp	F	1980 (38)	Unaffected	NT	Yes
Patient 3	<i>SPTLC1</i> p.Cys133Trp	M	1973 (45)	Unaffected	NT	Yes

* FLIO denotes fluorescence lifetime imaging ophthalmoscopy, NT not tested, and SPT serine palmitoyltransferase.

† The patients who received serine supplementation had been taking high-dose serine supplements for at least 1 year before examination.



levels of deoxy sphinganine were higher among patients with macular telangiectasia type 2 than among unaffected controls ($b=0.516$, $P=9.3\times 10^{-07}$), which suggests that the elevation in deoxy sphinganine levels in patients with macular telangiectasia type 2 is not driven by the greater number of patients with type 2 diabetes in this group (Table S1 in Supplementary Appendix 1).

Consistent with our previous findings,⁸ serine levels were significantly lower in serum specimens from patients with macular telangiectasia type 2 than among controls, by 20.6% on average ($b=-0.231$, $P=6.63\times 10^{-10}$) (Fig. 2D). In addition, levels of deoxy sphinganine showed the strongest correlations with levels of plasma serine ($b=-1.27$, $P=5.55\times 10^{-18}$) and alanine ($b=0.63$,

$P=7.59\times 10^{-05}$) (Fig. 2E and 2F), associations that remained significant when we controlled for other covariates and macular telangiectasia type 2 status. Patients with macular telangiectasia type 2 had total deoxysphinganine levels that were similar to, and in some cases higher than, those of patients with HSAN1, which suggested that reduced serine levels are sufficient to increase deoxysphinganine to disease-associated levels. These results show that reduced levels of circulating serine, regardless of the cause, result in accumulation of deoxysphinganine in serum in patients. (Additional details of these analyses are provided in Tables S6 through S10 and Figure S2A in Supplementary Appendix 1.)

We next determined the specific sphingolipid species that were represented in the total hydrolyzed deoxysphinganine pool and the way in which they were transported systemically (Fig. S2B and S2C in Supplementary Appendix 1). By comparing levels of free deoxysphinganine with levels of hydrolyzed deoxysphinganine (the sum of free deoxysphinganine plus deoxydihydroceramide), we found that nearly 90% of the pool of deoxysphinganine was derived from deoxydihydroceramide. When we measured the deoxysphinganine levels in fractionated serum we found that, similar to other sphingolipids,³⁰ deoxysphinganine was complexed with the low- and very-low-density lipoproteins, which suggests that the liver is the primary source of circulating deoxysphingolipids.

LOW SERINE LEVELS IN A MOUSE MODEL

We next tested whether low levels of circulating serine (macular telangiectasia type 2 phenotype) would be sufficient to increase tissue deoxysphingolipid levels. We fed 8-week-old male mice an isocaloric and isonitrogenous control diet or a diet that was depleted of serine and glycine (depletion of glycine prevents its compensatory conversion to serine³¹). We found no appreciable difference in food consumption, body weight, or body composition between the two groups of mice (Fig. S3A through S3D in Supplementary Appendix 1). Mice that were fed a serine- and glycine-free diet had lower serine levels throughout the day than did those that were fed the control diet ($P=9.3\times 10^{-14}$) (Fig. 3A).

The mice with low circulating serine levels had deoxysphinganine levels that were 3 times as high as those in the mice that were fed the

control diet ($P=0.002$) and had no change in sphinganine levels (Fig. 3B). We found a negative correlation between serine levels and deoxysphinganine levels ($r=-0.803$). The retina and retinal pigment epithelium from mice that were fed the serine- and glycine-free diet also had elevated deoxysphinganine levels ($P<0.001$ and $P=0.006$, respectively) (Fig. 3C and 3D). We examined the sciatic nerve and found a similar elevation in deoxysphinganine relative to the nerve in control mice ($P=0.04$) (Fig. 3E). The ratio of deoxysphinganine to sphinganine was also elevated in the plasma and tissues. (Additional details of these analyses are provided in Figure S3 in Supplementary Appendix 1.)

Retinal and peripheral sensory deficits developed in mice that were fed the serine- and glycine-free diet for 10 months. Electroretinographic measurements showed significant deficits in the photopic and flicker responses ($P=0.002$ and $P=0.005$, respectively) (Fig. 3F, 3G, and 3H, and Fig. S4 in Supplementary Appendix 1). Similar to a mouse model of HSAN1 in which mutant SPTLC1 was overexpressed,¹² mice that were fed the depleted diet also had an elevated thermal latency threshold ($P=0.005$) (Fig. 3I). A reduction in serine and glycine levels in plasma is sufficient to increase plasma and tissue levels of deoxysphingolipids and causes functional retinal and peripheral sensory deficits.

RETINAL TOXICITY OF DEOXYDIHYDROCERAMIDE

A characteristic late-stage manifestation of macular telangiectasia type 2 is the loss of photoreceptors in the macula³²; this process can be modeled in vitro with human induced pluripotent stem cell-derived retinal organoids, which are stratified retinal tissues containing most of the major neural retinal cell types, including functional photoreceptors and Müller glia (Fig. 4A).³³ Treatment of retinal organoids with deoxysphinganine induced photoreceptor apoptosis in a dose-dependent manner (Fig. 4B), with toxic effects at 50 nmol per liter ($P=0.03$), a concentration detected in patients with macular telangiectasia type 2 and HSAN1 (Fig. S2A in Supplementary Appendix 1). In contrast, toxic effects were not observed when organoids were treated with two distinct deoxysphingosine species.³⁴ Inhibition of ceramide synthase with fumonisins B1 prevented deoxysphinganine-induced cell death ($P=6\times 10^{-16}$) (Fig. 4C and 4D), indicating that the toxic effects

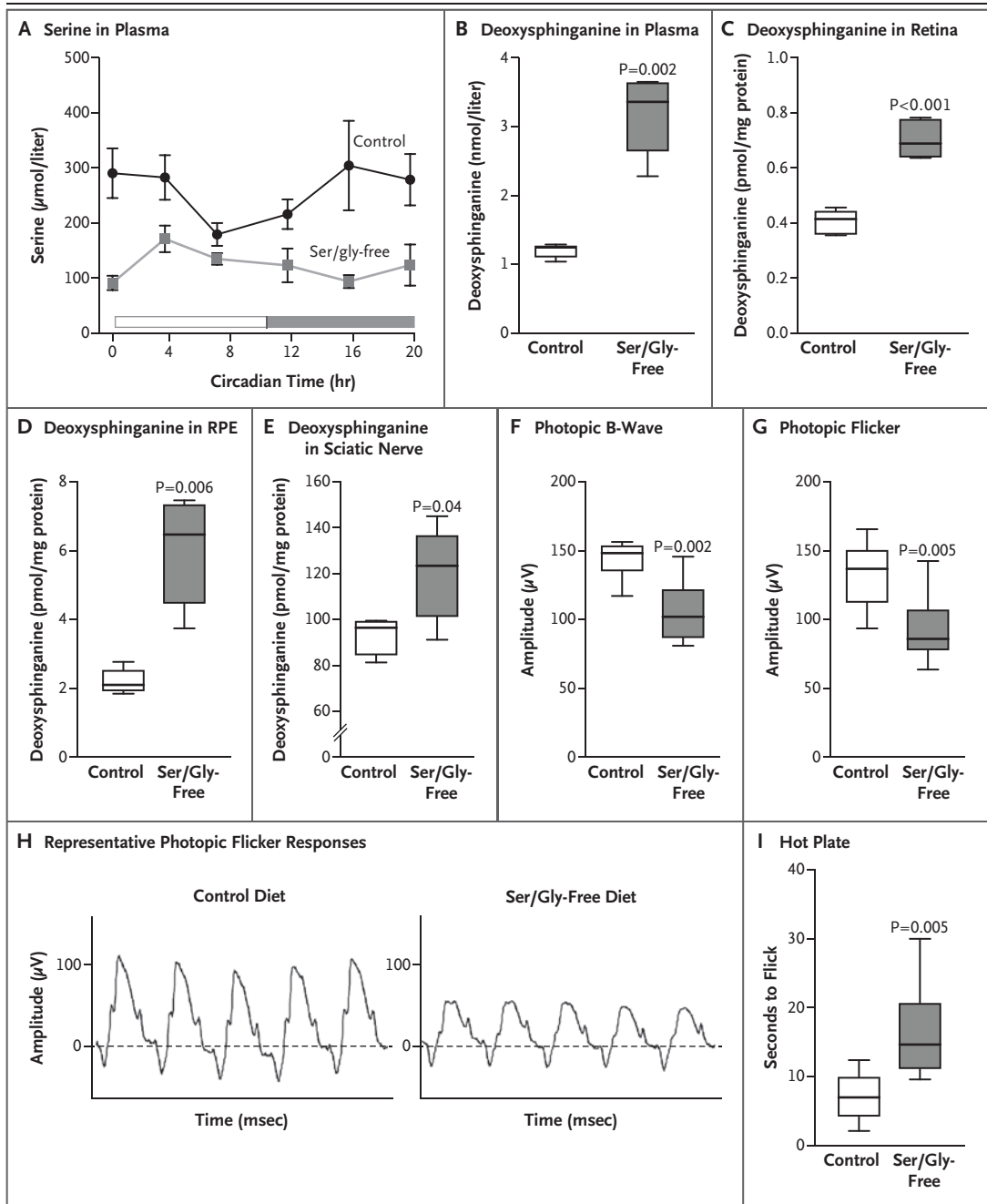
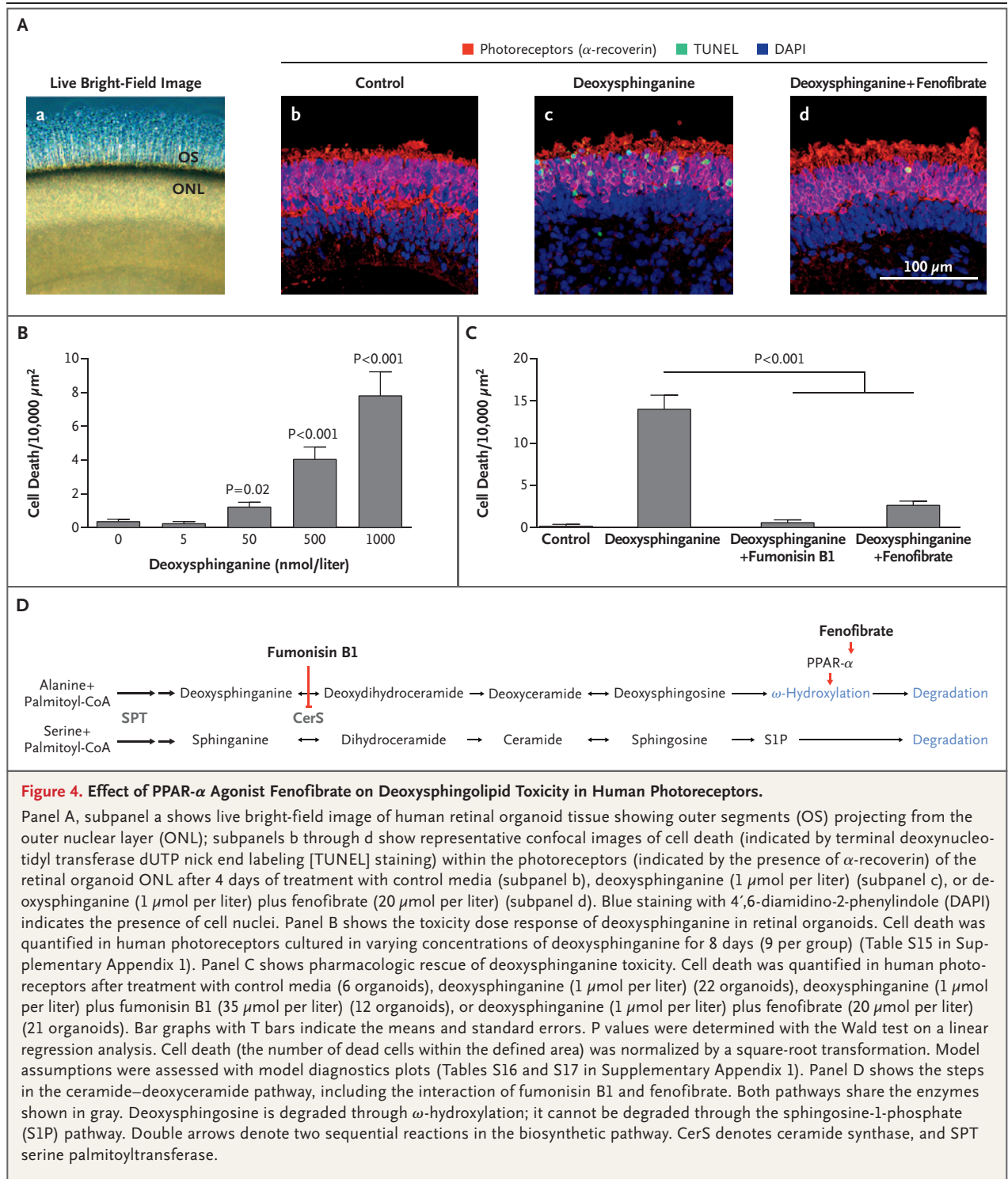


Figure 3. Serine and Deoxyseringanine Levels and Retinal and Peripheral Neural Defects in Wild-Type Mice.

Panel A shows serine levels in plasma measured in mice that were fed a control diet or serine- and glycine-free diet for 2 weeks (5 mice in each group). Panels B through E show the quantification of total hydrolyzed deoxyseringanine in plasma and in the indicated tissues in mice that were fed a control diet or a serine- and glycine-free diet for 3 months (5 mice in each group). Deoxyseringanine levels are normalized to the milligrams of tissue protein. RPE denotes retinal pigment epithelium. Panels F and G show electroretinographic (ERG) measurements of photopic responses to a flash in light-adapted mice that were fed a control or a serine- and glycine-free diet for 10 months (8 to 10 eyes in each group). Panel H shows representative photopic flicker responses from mice that were fed a control or a serine- and glycine-free diet. Panel I shows peripheral neural function evaluated by hot-plate assay indicating “time to flick” (i.e., time to a visible reaction to a thermal stimulus) in mice that were fed a control or a serine- and glycine-free diet for 10 months (8 mice in each group). Data represented by the box-and-whisker plots are the median, first and third quartile, and minimum and maximum values. P values were determined with Student’s t-test and corrected for multiple testing by the Benjamini–Hochberg procedure (Tables S14 and S15 in Supplementary Appendix 1).



were due to one or both of its downstream products, deoxydihydroceramide and deoxyceramide (Fig. 4D). To distinguish between these, we quantified ceramide species after treatment with deoxysphinganine, sphinganine, sphingosine, or

either species of deoxysphingosine and found that only the levels of deoxydihydroceramide correlated with toxicity. (Additional details of these analyses are provided in Figures S5 through S7 in Supplementary Appendix 1.)

FENOFIBRATE AND DEOXYSPHINGOLIPID-INDUCED RETINAL TOXICITY

We sought to ameliorate the toxic effects of deoxydihydroceramide with the use of the peroxisome proliferator-activated receptor α (PPAR- α) agonist fenofibrate (Fig. 4D). Fenofibrate has been shown to stimulate degradation of deoxysphingolipids in a human embryonic kidney cell line and has been used to reduce deoxysphinganine levels in patients with dyslipidemia.^{35,36} We found that concurrent treatment of retinal organoids with fenofibrate at a concentration of 20 μmol per liter decreased deoxysphinganine-induced cell death in photoreceptors by approximately 80% ($P=1.85\times 10^{-13}$) (Fig. 4A and 4C).

DISCUSSION

In addition to finding that altered amino acid and sphingolipid metabolism were the basis of the photoreceptor loss in patients with macular telangiectasia type 2, we have expanded the definition of diseases caused by variants in *SPTLC1* or *SPTLC2* and have shown a link between abnormal systemic serine metabolism and tissue-specific disease. HSN1-associated variants in these genes lead to pathologic accumulation of deoxysphinganine; our data show that these mutations also cause macular telangiectasia type 2. The vast majority of patients with macular telangiectasia type 2 do not have variants in *SPTLC1* or *SPTLC2*, but these patients do have low serine levels and elevated deoxysphingolipid levels. Reducing circulating serine in mice is sufficient to increase deoxysphingolipid levels and cause functional defects in the retina and peripheral nerves. We therefore conclude that elevated deoxysphingolipid levels can cause macular disease in the broader population of patients with macular telangiectasia type 2, as well as in patients with HSN1.

We do not know why serine levels are systemically low in patients with macular telangiectasia type 2. Given that serine is central to numerous metabolic pathways, the genetic regulators are probably diverse. A genomewide association study identified loci associated with the condition within or near two of the three genes involved in de novo serine synthesis — *PHGDH* and *PSPH⁸* — which supports speculation that perhaps serine synthesis is impaired in some patients.

Perhaps, as well, some patients have elevated levels of deoxysphingolipids because of high alanine levels or impaired lipid degradation. The multiple means of regulating serine and deoxysphingolipid levels may reflect the genetic heterogeneity observed in macular telangiectasia type 2. Variations in environmental factors, such as diet, could also explain the variable penetrance of macular telangiectasia type 2 in families.

Although elevated levels of deoxysphingolipids are known to be cytotoxic,^{10,13,28,37} the mechanism of their toxicity is not fully understood. Deoxysphingolipids have been reported to disrupt mitochondrial function.¹⁶ In this study, we have shown that these lipids are toxic to human photoreceptors and identified deoxydihydroceramide as the main neurotoxic species. It accounted for nearly 90% of the hydrolyzed deoxysphinganine measurements in serum from patients. Further work is needed to understand the mechanism of retinal toxicity and the potential involvement of other sphingolipid metabolites. Although deoxysphinganine accumulation is observed systemically, it is not clear why the macular region of the retina and the extremities of the somatosensory nervous system are preferentially affected, but their unique metabolic demands could make them particularly vulnerable.

Abnormal serine metabolism, leading to increased levels of deoxysphingolipids, may represent a broader “serineopathy” class of diseases that includes both retinal and peripheral neuropathies, and so it might be expected that patients with macular telangiectasia type 2 would also be at risk for peripheral neuropathies. Elevated deoxysphingolipid levels have been reported in patients with diabetes and may contribute to diabetic retinopathy and peripheral neuropathy,²⁸ which are common complications of diabetes. Although deoxysphingolipid levels can be reduced by systemically administering serine or fenofibrate,^{18,36} we caution against prescribing serine or fenofibrate to patients with macular telangiectasia type 2, given the complex genetic etiology of the condition and the genetic diversity in the patient population.

We have used a detailed patient registry, genetic and metabolomic analyses, and mouse and organoid models to uncover a link among macular telangiectasia type 2, HSN1, and deoxysphingolipids. In so doing, we established a connection

between central and peripheral neuropathies, as well as between plasma amino acid levels and these disorders.

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