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G. 知的所有権の取得状況

1 特許取得

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2 実用新案登録

該当なし

3 その他

該当なし

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研究成果の刊行物・別刷

nature genetics

A common variant mapping to *CACNA1A* is associated with susceptibility to exfoliation syndrome

Exfoliation syndrome (XFS) is the most common recognizable cause of open-angle glaucoma worldwide. To better understand the etiology of XFS, we conducted a genome-wide association study (GWAS) of 1,484 cases and 1,188 controls from Japan and followed up the most significant findings in a further 6,901 cases and 20,727 controls from 17 countries across 6 continents. We discovered a genome-wide significant association between a new locus (*CACNA1A* rs4926244) and increased susceptibility to XFS (odds ratio (OR) = 1.16, $P = 3.36 \times 10^{-11}$). Although we also confirmed overwhelming association at the *LOXL1* locus, the key SNP marker (*LOXL1* rs4886776) demonstrated allelic reversal depending on the ancestry group (Japanese: $OR_{A\ allele} = 9.87$, $P = 2.13 \times 10^{-217}$; non-Japanese: $OR_{A\ allele} = 0.49$, $P = 2.35 \times 10^{-31}$). Our findings represent the first genetic locus outside of *LOXL1* surpassing genome-wide significance for XFS and provide insight into the biology and pathogenesis of the disease.

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XFS is a generalized disorder of the extracellular matrix that manifests most conspicuously in the eye. The exfoliation material consists of cross-linked, amyloid-like fibrillar material and glycoproteins. Apart from in ocular tissues, this material deposits around blood vessels, particularly in association with elastic connective tissue, and can be found in other organs[1]. The accumulation of exfoliation material deposits and pigment in the trabecular meshwork can damage this tissue and impede the drainage of aqueous humor from the eye, thus resulting in elevated intraocular pressure and glaucomatous optic neuropathy. Exfoliation glaucoma is the most serious known complication of XFS[2].

The first GWAS of XFS was reported in 2007 and successfully identified *LOXL1* as a major susceptibility locus[3]. Since then, multiple studies have uniformly corroborated the association of genetic variants of *LOXL1* with XFS[4–21]. However, data from these studies showed that associated alleles for *LOXL1* SNPs frequently undergo allelic reversal depending on ancestry group[22]. These findings suggest that complex genetic mechanisms are present in XFS pathogenesis and that additional susceptibility loci for XFS remain to be identified. We assembled an international, multi-institutional collaborative effort across 6 continents and 17 countries to conduct a GWAS discovery and 2-stage replication study of XFS (Online Methods, **Supplementary Fig. 1** and **Supplementary Table 1**). Participating subjects provided written informed consent under the oversight of all local institutional review boards in accordance with the tenets of the Declaration of Helsinki.

For the GWAS discovery stage, we genotyped 717,991 SNP markers in 1,578 Japanese subjects with XFS (cases) and 1,215 controls using the Illumina HumanOmniExpress-12 v1.0 DNA analysis BeadChip microarray. Control subjects were drawn from the same hospital where the XFS cases were first identified. A total of 1,484 cases and 1,188 controls passed quality control filters for call rate, relatedness, heterozygosity and ancestry (see the Online Methods for details on quality control) and were included for downstream association analysis. Multiple markers in strong linkage disequilibrium (LD) at the *LOXL1* locus showed strong evidence of association with XFS (**Supplementary Fig. 2a**), with rs4886776 ($P = 7.37 \times 10^{-137}$) serving as the sentinel SNP.

A total of 66 SNPs outside of *LOXL1* showed evidence of association with XFS surpassing $P < 1 \times 10^{-4}$ at the GWAS discovery stage. We thus designed validation assays for these 66 SNP markers, together with *LOXL1* rs4886776, and genotyped them in a follow-up collection of 2,628 XFS cases and 8,947 controls drawn from 9 countries (stage 1 validation; **Supplementary Table 1**). For each SNP examined, we conducted a fixed-effects meta-analysis to summarize the observations across the nine studies. One SNP marker (rs4926244) mapping within the *CACNA1A* gene was associated in the GWAS discovery stage at $P = 5.50 \times 10^{-5}$ ($OR_{G\ allele} = 1.29$) and was also significantly associated in the validation stage ($OR_{G\ allele} = 1.17$, $P = 4.17 \times 10^{-5}$). For rs4926244, meta-analysis of both the discovery and validation stages showed a genome-wide significant association ($OR_{G\ allele} = 1.20$, $P = 2.45 \times 10^{-8}$) (**Fig. 1, Supplementary Fig. 2b** and **Supplementary Table 2**). Results for all 67 SNP markers from the GWAS discovery and stage 1 replication are shown in **Supplementary Table 2**. We did not observe consistent evidence of association at *CNTNAP2*, a locus previously reported to associate with XFS in a pooled GWAS analysis[23], or at other previously reported candidate genes (**Supplementary Table 3**).

We subjected *CACNA1A* rs4926244 to further technical scrutiny in a third, independent data set consisting of 4,273 XFS cases and 11,780 controls drawn from 8 additional countries (stage 2 replication; **Supplementary Table 1**). The association maintained significance, consistent with the findings from the two previous stages ($OR_{G\ allele} = 1.13$, $P = 1.14 \times 10^{-4}$). Together, the combined discovery and 2-stage replication collections consisting of 8,385 XFS cases and 21,915 controls provided evidence for association of the minor G allele at rs4926244 with XFS ($P = 3.36 \times 10^{-11}$). These data suggest that risk for XFS increases by approximately 1.16-fold for each copy of the minor G allele (**Fig. 1** and **Supplementary Table 4**). This association appeared to be consistent, with minimal heterogeneity

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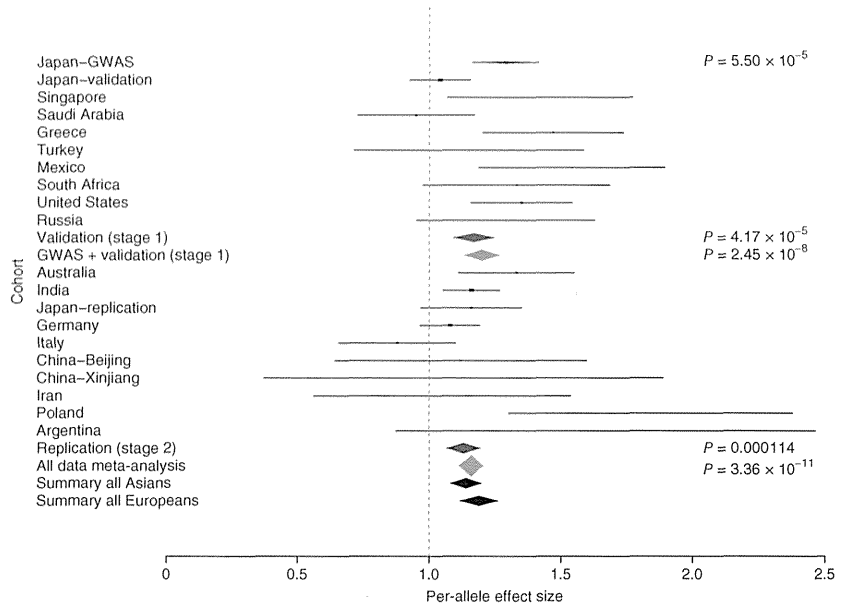

Figure 1 Forest plot for the associations between *CACNA1A* rs4926244 and XFS in discovery and follow-up case-control collections. Black lines denote the 95% confidence intervals of the OR estimates for each collection. Diamonds denote summary results for the GWAS, validation and replication stages (blue), as well as for meta-analysis of the GWAS and validation stages and meta-analysis of data from all collections (red). Asian- and European-ancestry summary results are represented by black diamonds.

with stratification for Asian ($OR_{G\ allele}$ = 1.14, $P = 7.46 \times 10^{-6}$), European ($OR_{G\ allele}$ = 1.19, $P = 1.90 \times 10^{-6}$) or South African ($OR_{G\ allele}$ = 1.33, P = 0.11) ancestry groups (P value for heterogeneity (P_{het}) = 0.5, I^2 index for heterogeneity = 0%) (**Fig. 1**).

SNP rs4926244 resides within an intronic region near the 3′ end of *CACNA1A*. It is closely flanked by recombination events (**Fig. 2**) and is confined to its own LD block (**Supplementary Fig. 3**). We did not observe association with any genetic marker surpassing the nominal threshold of $P < 0.001$ outside of this region (**Fig. 2**)[24]. We next performed imputation for ungenotyped SNPs at the *CACNA1A* locus on the basis of 1000 Genomes Project cosmopolitan data using the Phase 3 release (June 2014; Online Methods) across the GWAS discovery collection. We were able to successfully impute 5,602 SNPs across the *CACNA1A* locus. However, subsequent association analysis using the imputed SNPs did not identify additional genetic associations that surpassed the statistical significance of rs4926244 (**Supplementary Fig. 4**). Notably, the most significant SNPs emerging from the cosmopolitan imputation analysis were intronic and all showed moderate-to-high correlation with rs4926244 (**Supplementary Table 5**). None of these correlated SNP markers were located in strong motifs for transcription factor binding sites as identified by the Encyclopedia of DNA Elements (ENCODE). They also did not tag any common nonsynonymous variants in *CACNA1A* (**Supplementary Table 6**). Haplotype association analysis assessing SNPs in a two-, three- or four-marker sliding window did not find evidence of an association surpassing that observed for rs4926244 (lowest haplotype P = 0.00021; **Supplementary Table 7**), and we further note that all but one haplotype showing evidence of association exceeding $P < 0.0005$ in the GWAS data set contained SNP rs4926244 (**Supplementary Table 7**). These findings suggest that rs4926244 is likely driving the common-variant haplotype association results and that detailed fine mapping of this locus using deep resequencing may be required. Examination of a recently available large-scale expression quantitative trait locus (eQTL) mapping database indicated that the G risk allele at rs4926244 is modestly correlated with lower *CACNA1A* mRNA levels in peripheral blood cells (z = −3.00, P = 0.0027), suggesting that it may influence XFS risk through an effect on *CACNA1A* expression[25]. Further work will be needed to evaluate its effect in human ocular tissues.

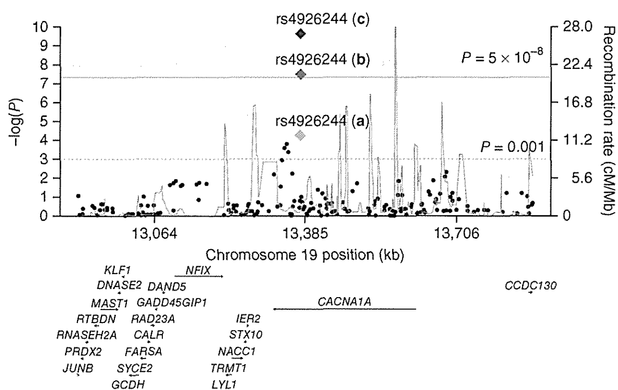

Figure 2 Regional association and recombination rate plot for the *CACNA1A* rs4926244 locus. The left *y* axis represents $-\log_{10}$ (P values) for association with XFS, and the right *y* axis represents the recombination rate. The *x* axis represents base-pair positions along the chromosome (human genome Build 37). Diamonds denote the summary results for each experimental stage. (**a**) GWAS discovery. (**b**) Meta-analysis between the GWAS discovery and validation stages. (**c**) Meta-analysis between the GWAS discovery, validation and replication stages.

Initial analysis of the *LOXL1* locus in the GWAS discovery data set comprising individuals of Japanese descent demonstrated strong association at rs4886776 ($OR_{A\ allele}$ = 8.31, $P = 7.37 \times 10^{-137}$). The strength of this association vastly exceeded that of marker rs3825942 (responsible for a p.Gly153Asp substitution encoded in exon 1 of *LOXL1*), which has been the most widely tested and reported SNP association before this analysis[22]. Performing the analysis after conditioning for the allele dosage at rs4886776 extinguished the signal of association for every other genetic marker within the *LOXL1* locus. Conversely, conditioning the analysis for allele dosage at rs3825942 still resulted in genome-wide significant association at many of the other *LOXL1* SNPs, including rs4886776 (**Supplementary Table 8**). These data suggest that, within the Japanese GWAS discovery set, the observed association at *LOXL1* can be attributed to rs4886776 alone. We note that rs4886776 is in high LD with rs1048661 (r^2 = 0.98 in 1000 Genomes Project Asians), a SNP that is responsible for another nonsynonymous substitution in *LOXL1* (encoding p.Arg141Leu) but that was not directly genotyped in our data set. However, we were able to successfully impute rs1048661 in our GWAS discovery data set, and we confirmed its strong association with XFS ($OR_{T\ allele}$ = 8.13, $P = 1.32 \times 10^{-126}$). SNP rs1048661 has previously been reported to show strong association with XFS in multiple populations, although

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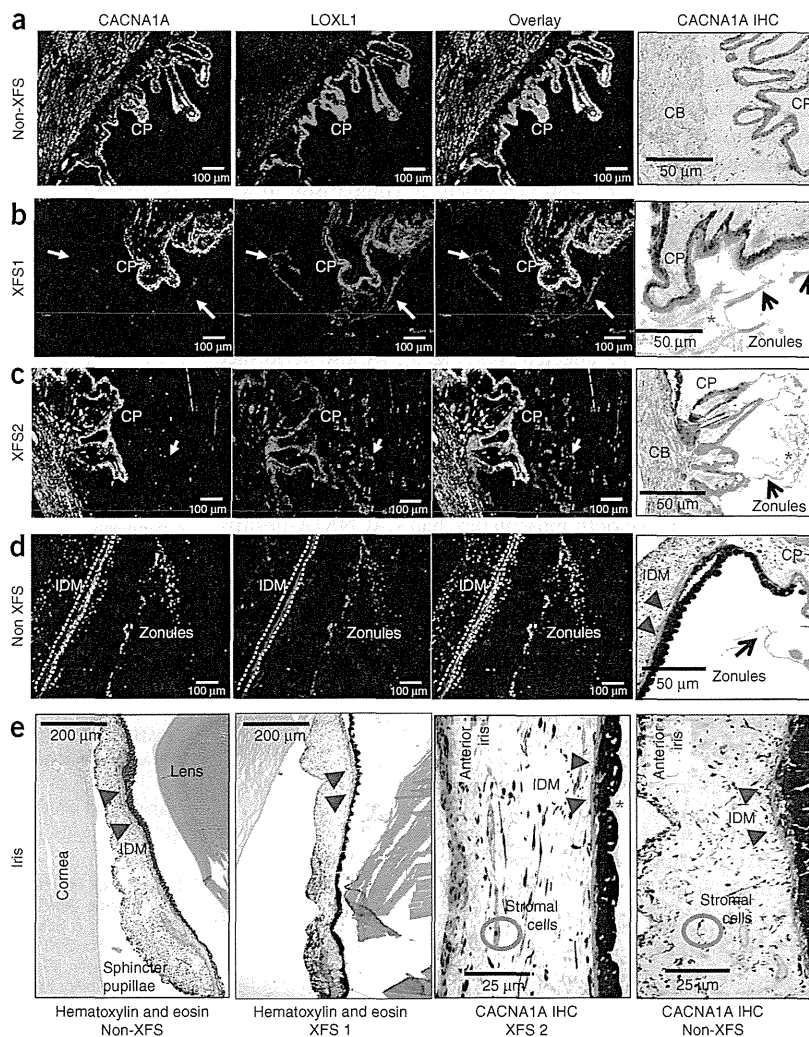

Figure 3 CACNA1A and LOXL1 protein expression and light-microscopy analysis in XFS and non-XFS control eyes. (**a**–**d**) Immunolocalization of CACNA1A in human non-XFS globes (**a**,**d**) and in XFS1 (**b**) and XFS2 (**c**) globes with XFS shows CACNA1A-positive immunoreactivity in the smooth musculature of the ciliary body (CB) and pigmented and non-pigmented ciliary process (CP) epithelium, with variable staining in the zonules (white and black arrows; exfoliated material, green asterisks). In contrast, LOXL1 immunoreactivity is present only in the exfoliated material and the ciliary process epithelium (zonules, white arrows). Double-immunofluorescence analysis (overlay) shows colocalization of CACNA1A and LOXL1 in the non-pigmented and pigmented epithelium of the ciliary process but not in the ciliary body smooth musculature or the zonules (white arrows). Light-microscopy comparison of non-XFS and XFS irides identifies the typical XFS findings of exfoliated material (green asterisks) on the posterior iris and atrophic iris pigment epithelium with possible atrophy of the iris dilator muscle (IDM; blue arrowheads) in XFS irides. The sphincter pupillae in non-XFS and XFS eyes show negligible differences. (**d**,**e**) CACNA1A-positive immunoreactivity is also seen in the anterior iris border, iris stromal cells, and iris dilator (blue arrowheads) and sphincter muscles as well as in the iris pigmented epithelium in both XFS (**e**) and non-XFS (**d**,**e**) irides. Stromal cells are highlighted by the blue ovals in **e**. IHC, immunohistochemistry.

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the risk allele is reversed depending on which ancestry group is being studied[11,22]. This SNP is also in LD with several other *LOXL1* SNPs located in potential transcription factor binding sites (**Supplementary Table 6**)[26,27].

SNPs rs4886776 and rs3825942 are in moderate pairwise LD ($r^2 = 0.23$). When we genotyped rs4886776 for the 2,628 XFS cases and 8,947 controls from stage 1 validation (**Supplementary Table 1**), we noted very strong evidence of consistent association for Japanese individuals ($OR_{A\ allele} = 21.7$, $P = 1.54 \times 10^{-135}$), leading to an overwhelmingly significant association in the Japanese cases and controls analyzed ($OR_{A\ allele} = 9.87$, $P = 2.13 \times 10^{-217}$). Strikingly, in non-Japanese populations, the direction of the association was opposite to that seen in the Japanese ($OR_{A\ allele} = 0.49$, $P = 2.35 \times 10^{-31}$) (**Supplementary Fig. 5**). Such a scenario echoes recently reported observations for the reversed effect of rs3825942 on XFS risk in South Africans and suggests that the genetic mechanism whereby *LOXL1* exerts its effect on individual susceptibility to XFS is complex[22]. We failed to detect any evidence of statistically significant interaction between *CACNA1A* rs4926244 and the sentinel *LOXL1* polymorphisms, suggesting that these loci affect XFS risk via distinct biological pathways.

CACNA1A encodes the α1A subunit of the type P/Q voltage-dependent calcium channel. Calcium channels are responsible for the transport of calcium ions across cell membranes and have a key role in a cell's ability to generate and transmit electrical signals. Previous electron microscopy studies on human eyes with XFS showed the presence of high calcium concentrations in direct association with aggregating XFS fibrils[28]. In addition, it is well known that fibrillin uses calcium to form stable aggregates[29]. Thus, it can be hypothesized that the altered function of a calcium channel could lead to alterations in calcium concentrations that might facilitate the formation of XFS aggregates.

As there is a paucity of information on CACNA1A expression in the eye, we examined the mRNA expression profile of *CACNA1A* and protein expression of CACNA1A in a variety of human ocular tissues and cell lines, respectively (**Supplementary Fig. 6**). We detected *CACNA1A* mRNA expression in all of the ocular tissues we studied, with the exception of the optic nerve head (**Supplementary Fig. 6a**). Expression of different CACNA1A isoforms appears to be higher in human ocular tissue–derived cells than in cells of non-ocular origin (**Supplementary Fig. 6b**). We also performed immunofluorescence and immunohistochemistry analysis on adult human eyes and observed positive immunoreactivity for CACNA1A in multiple human ocular tissues (**Fig. 3**, and **Supplementary Figs. 7** and **8**). The distribution of CACNA1A was similar in human ocular tissues from individuals with or without XFS (**Fig. 3**, and **Supplementary Figs. 8** and **9**). Positive staining and localization of CACNA1A in the human eye was further corroborated by immunofluorescence microscopy analysis in mouse eyes (**Supplementary Fig. 10**). In human eyes, we observed positive CACNA1A immunoreactivity in the ciliary body and iris (**Fig. 3**). We also found positive staining for CACNA1A in

the anterior lens epithelium but not in the acellular capsule and the cornea (**Supplementary Figs. 7** and **9**). The optic nerve glia and vascular endothelial cells also showed positive immunoreactivity for CACNA1A (**Supplementary Fig. 9**). For the retina, we observed strong, diffuse CACNA1A staining in the photoreceptor inner segments, inner nuclear layer (INL) and outer nuclear layer (ONL), and nerve fiber layer (NFL) of non-XFS globes in comparison to XFS globes, where we observed focal and patchy immunostaining of the inner segments, ONL, INL and NFL. Light-microscopy comparison of the irides in XFS-affected eyes against eyes without XFS identified typical XFS findings of exfoliated material on the posterior iris and atrophic iris pigment epithelium, as well as possible atrophy of the iris dilator muscle, in XFS-affected eyes (**Fig. 3**). We also performed double-immunofluorescence microscopy for CACNA1A and LOXL1 in human eyes with and without XFS and observed colocalization of CACNA1A and LOXL1 only in the epithelium of the ciliary processes. The exfoliated material in eyes with XFS showed LOXL1-positive staining with negligible CACNA1A immunoreactivity. The ciliary body and iris smooth musculature had CACNA1A-positive immunostaining but were negative for LOXL1 staining in eyes with and without XFS (**Fig. 3**). This observation raises the possibility that CACNA1A and LOXL1 contribute to XFS pathology through different mechanisms at different ocular sites.

In summary, we have identified a susceptibility locus for XFS mapping to *CACNA1A* using a three-stage GWAS study design. Further investigation of this locus is now warranted to uncover the mechanisms through which CACNA1A affects individual susceptibility to XFS.

URLs. Illumina, http://www.illumina.com/; Sequenom, https://www.sequenom.com/; Applied Biosystems, http://www.appliedbiosystems.com/; PLINK, http://pngu.mgh.harvard.edu/~purcell/plink/; R statistical program package, http://www.r-project.org/; IMPUTE2, http://mathgen.stats.ox.ac.uk/impute/impute_v2.html.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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T.A., M.O. and C.-C.K. conceived the project. M.O., T.M., R.R.A., A.H., S.N., J.E.C., A.W.H., D.A.M., P.M., J.J.W., Y.S.A., J.C.Z., Y.N., T.Z., M.P., L.J., Y.X.W., S.W., D.P., P.G.S., Y.I., R.S.K., M.U., S. Manabe, K.H., S. Kazama, R.I., Y.M., K. Miyata, K.S., T.H., E.C., K.I., S.I., A.Y., M.Y., Y.K., M.A., T.O., T. Sakurai, T. Sugimoto, H.C., K.Y., S.Y.A., E.A.O., S.A.A.-O., O.O., L.A.-J., S.A.S., Y.Y., Ç.O., M.R.K., A.N.B., S.Y., E.L.A., E.K.-J., U.L., P.C., R.M.R., A.Z., T.C., R. Ramakrishnan, K.N., R.V., P.Z., X.C., D.G.-V., S.A.P., R.H., S.-L.H., U.-C.W.-L., C.M., U.S.-S., S. Moebus, N. Weisschuh, R.S., A.G., I.L., J.G.C., M.C., Q.Y., V.V., P. Founti, A.C., A.L., E.A., A.L.C., M.R.W., D.J.R., I.M.-B., K. Mori, S. Heegaard, W.L.M.A., J.B.J., L.X., J.M.L., F.L., N. Wang, P. Frezzotti, S. Kinoshita, J.H.F., M.I., D.P.E., L.R.P., T.K., J.L.W., F.T., N.Y. and R. Ritch conducted patient recruitment and phenotyping. Z.L., S.U., M.K., K.P.B., M.A.B., J.J.W., Y.G., K.-Y.T., L.H., P.S., W.Y.M., S.Q.P., B.Z., J.S., N.Z., Z.Y. and S.V. performed genotyping experiments. J.M.H., A.S.Y.C., M.C.L., E.N.V., G.R.H. and S.W.M.J. led and performed immunohistochemistry and immunofluorescence experiments. Z.L., K.P.B., R.A.F., P.L., K.K.A.-A., L.A.S., L.H., K.S.S., J.N.F., M.N., F.M., N.G., M.M., S.U., M.K., Y.Y.T., J.H.K., A.E.A.K., S. Herms, Y.L., K.T., B.Z., J.S., N.Z., S.V., Z.Y., G.R.H., P.S., A.C.O., F.P. and A.G. performed analysis. E.N.V., T.Y.W., C.Y.C., P.S., A.M.H., M.M.N., B.C., E.S., M.S. and A.R. contributed genetic and genotyping data from control populations. The manuscript was drafted by C.-C.K., with critical input from T.A., R.R.A., L.R.P., J.L.W., F.P., F.T., M.D., S.W.M.J., R. Ritch and M.A.H. The manuscript was approved by all authors. C.-C.K. was responsible for obtaining financial support for this study.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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