Evaluation of the genetic basis of familial-associated early-onset hematologic cancers in an ancestral/ethnically diverse population

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Abstract

Genetic predisposition to hematologic malignancies has historically been addressed utilizing patients recruited from clinical trials and pedigrees constructed at major treatment centers. Such efforts leave unexplored the genetic basis of variations in risk by race/ethnic group shown in population-based surveillance data where cancer registration, compulsory by law, delivers universal enrollment. To address this, we performed exome sequencing on DNA isolated from newborn bloodspots derived from sibling pairs with early-onset cancers across California in which at least one of the siblings developed a hematologic cancer, using unbiased recruitment from the full state population. We identified pathogenic/likely pathogenic (P/LP) variants among 1,172 selected cancer genes that were private or present at low allele frequencies in reference populations. Within 64 subjects from 32 families, we found 9 LP variants shared between siblings, and an additional 7 such variants in singleton children (not shared with their sibling). In 8 of the shared cases, the ancestral origin of the local haplotype that carries P/LP variants matched the dominant global ancestry of study participant families. This was the case for Latino sibling pairs on *FLG* and *CBLB*, non-Latino White sibling pairs in *TP53* and *NOD2*, and a shared *GATA2* variant for a non-Latino Black sibling pair. A new inherited mutation in *HABP2* was identified in a sibling pair, one with diffuse large B-cell lymphoma and the other with neuroblastoma. Overall, the profile of P/LP germline variants across ancestral/ethnic groups suggests that rare alleles contributing to hematologic diseases originate within their race/ethnic origin parental populations, demonstrating the value of this discovery process in diverse, population-based registries.

Introduction

Hematologic malignancies (including leukemias, lymphomas, and multiple myeloma) are the most commonly diagnosed early-onset cancers among children, adolescents, and young adults.[1] Inherited and *de novo* mutation of genes within critical cell development and growth/signaling pathways are central oncogenic events in the pathogenesis of hematologic cancers.[2] Pathogenic/likely pathogenic (P/LP) germline variants were identified in approximately 10% of pediatric hematologic cancer patients regardless of family history.[3-6] The risk of early-onset cancers (of any type) diagnosed under 26 years of age is 2.97 times higher among siblings and mothers who have a proband with hematologic cancer in the same family,[7] indicating that inherited germline variants may contribute to this excessive cancer risk. This risk varies among ancestral/ethnic groups,[7] suggesting that predisposition variants may vary by identity or frequency among groups.

Among early-onset hematologic malignancies, acute lymphoblastic leukemia is the most common, accounting for approximately 25% of all cancers diagnosed in children; and other lymphoid malignancies account for an additional 10% of all cancers.[1,8] In our examination of linked population registries in California, the relative early-onset cancer risk is 2.87 times higher among siblings and mothers given a proband with leukemia, and 4.66 times higher given a proband with lymphoma.[7] Acute lymphoblastic leukemia (ALL) is the most common leukemia in children and young adults. Recent studies have identified deleterious germline variants in *TP53, PAX5, IKZF1*, and *ETV6* as risk factors for ALL[9-11] but have not assessed the spectrum of deleterious germline variants among ancestral groups or in individuals

with a family history identified in a population-based registry. Concerning the elevated familial risk of lymphoid malignancies other than leukemia that our group has observed in California,[7] previous studies have reported similar results: that first-degree relatives of patients with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), or chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) among European origin populations have approximately 1.7 times, 3.1 times, and 8.5 times higher risk of developing these malignancies, respectively.[12-17] Rare variants associated with familial-associated lymphoma risk, however, have not been studied extensively.[18]

The risk of hematologic cancers varies by ancestral/ethnic group. In California, Latino individuals have a higher incidence of ALL compared to those of other ancestral/ethnic groups across all ages;[19] however, the highest familial risk (identified by families with 2 or more independent sibling cancers) was found among non-Latino Asian/Pacific Islanders (NLAPI).[7] For lymphomas diagnosed under 19 years of age, the incidence among non-Latino White (NLW) subjects is higher than subjects of other ancestral/ethnic groups.[7] However, the variation in germline predisposition that may drive this difference in risk by ancestral/ethnic group has not been formally addressed. Standard US state-based population registries may be useful to study rare genetic predispositions in an objective, "real world" population-based manner when biological samples are available. Here, we utilize linked cancer population registries in California along with the California Biobank to identify the nature and ancestral origin of rare P/LP germline variants that may explain this variation in cancer risk.

Methods

Our study methods were reviewed and approved by the Committee for Protection of Human Subjects (IRB) of the State of California. Cancer patients were derived from linked population-based registries in California, as previously described.[7] Briefly, the dataset was created by linking information from the California Cancer Registry (CCR) and California Birth Statistical Master File. The linked dataset encompassed all cancer cases comprehensively diagnosed in individuals aged 0-26 years old (since 26 is the oldest age for which it was possible to perform this linkage at the time of this work), and their sibling's and their mother's cancers also captured within this registry. To study the rare genetic predispositions in association with hematologic cancers, we first identified all sibling pairs with cancer in the database. For all individuals with hematologic cancers (leukemia or lymphoma) and a sibling with cancer (of any type, excluding any iatrogenic cancers), we processed the pair for sequencing. Overall, 70 patients from 35 families were eligible for inclusion.

DNA preparation and sequencing, and mapping and variant identification were performed as explained in the *Online Supplementary Methods*. The GATK pipeline for germline short variant calling was performed, with variant filtering as appropriate. Presence of Down syndrome (DS) was assessed by chromosome 21 copy number normalized to all other chromosomes. Pathogenicity of variants in 1,172 genes (*Online Supplementary Table S1*) was initially assessed using informatic tools (Varsome, PeCanPie), followed by strict manual curation of all identified alleles by ACMG/AMP guidelines.

The ancestral identity of each individual was assessed by matching local haplotypes with one of 5 Earth superpopulations: Latino (LAT), European (EUR), East Asian (EAS), African (AFR), South Asian (SAS). The informatic tool RFMix was used for this purpose, and the global ancestry of each individual was calculated by summing up the ancestral components of each of the haplotypes for the entire genome.

Results

Demographics of study participants

Among the 70 patients eligible for inclusion, 67 samples had adequate DNA for genotyping, and 64 of the 67 samples were sibling pairs from the same family and were included in the genetic analyses. The 64 subjects were from 32 families, among which 12 (38%) were LAT and 10 (31%) were non-Latino White (NLW) families (Table 1). Including parents and all healthy or diseased children, the average size of each LAT family was 4.92 people/family and the average size of NLW families was 6.10 people/family. One out of the 32 families had a mother diagnosed with cancer (desmoplastic small round cell tumor) in her twenties; we note that given the recruitment period of 1989-2015 we have a limited available follow-up time to track adult cancer in parents. We do not report age of onset of any cancer case to protect confidentiality of the families evaluated in this study. One subject (#534, family #2) was identified to have DS (# chr21 reads= 917228; population mean and Standard Deviation [SD] of chr21 = 651691+/-128812).

Pathogenic/likely pathogenic and variants of uncertain significance

The mean sequencing coverage across subjects was 69.1 (range: 37.2-98.7) (*Online Supplementary Table S2*). Our initial software-guided curation yielded 14 unique P/LP variants. Upon further refined manual curation, 5 P/LP variants were reclassified as variants of uncertain significance (VUS), leaving 9 rare P/LP variants shared between siblings among 8 sibling pairs (*Online Supplementary Table S3*), and 105 rare VUS that are shared between siblings among the 32 families (*Online Supplementary Table S4*). Notably, along with demoting 5 LP variants to VUS, manual curation rescued one VUS to be LP *(HABP2)*, and reclassified another 23 VUS to be LB (likely benign; *Online Supplementary Table S4*). Among the P/LP variants, one (11%) was found in LAT families, 2 (22%) were found in NLW families, 2 (22%) were found in non-Latino

Black (NLB) families, 2 (33%) were found in non-Latino Asian/Pacific Islander (NLAPI) families, and one (11%) was found in a non-Latino American Indian/Alaskan Native (NLAIAN) family. Among the VUS, 41 (39%) were found in LAT families, 21 (22%) were found in NLW families, 10 (10%) were found in NLB families, 27 (28%) were found in NLAPI families, and one (1%) was found in a NLAIAN family (Table 2). In the LAT families, P/LP variants were detected in *ATM* (NM_000051.3:c.3158dup; one sibling had T-cell leukemia and the other had diffuse large B-cell lymphoma) in family #27. For NLW families, P/LP variants were detected on *TP53* (family #6, NM_000546.5:c.586C>T; one sibling with acute leukemia, not otherwise specified [NOS], and the other with signet ring carcinoma), and *NOD2* (family #25, NM_022162.2:c.1515dup; both siblings diagnosed with HL NOS). For NLB families, P/LP variants were detected on *GATA2* (family #15, NM_001145661.1:c.1009C>T; one sibling AMML-M4 and second sibling, AMKL-M7) and *NOD2* (family #35, NM_022162.2:c.1515dup; both siblings with Burkitt cell leukemia). In separate NLAPI families, P/LP variants were detected on *FLG* (family #2, NM_002016.1:c.3321del; HL and AMKL-M7), and *CBLB* (family #21, NM_170662.4:c.2307del; large B-cell lymphoma and neuroblastoma). The siblings in this family also shared an additional nonsense variant in *HABP2*. For one NLAIAN family (#29), a P/LP variant was detected on *SBF2* (NM_030962.3:c.4400del; one sibling with acute lymphoblastic leukemia NOS and the other sibling with hepatoblastoma) (*Online Supplementary Table S4*).

In addition, we identified 7 rare P/LP variants that are not shared between the 2 siblings. In 4 LAT subjects without any P/LP variants shared with siblings, these included a nonsense variant in *AMER1* (NM_152424.3:c.28C>T), a frameshift deletion in *HLTF* (NM_003071.3:c.1967del), and missense variants in *GJB2* (NM_004004.5:c.596C>T) and *PINK1* (NM_032409.2:c.1040T>C) (*Online Supplementary Table S5*). In one NLW subject diagnosed with a malignant teratoma, we found a non-shared nonsense variant in *SMARCA4* (NM_001128849.1:c.4038G>A). In an NLB subject who developed acute megakaryoblastic leukemia (AMKL), and who also shared a P/LP variant in *GATA2* with their sibling who developed acute myeloid leukemia (family #15), a non-shared nonsense variant was identified in *FAT1* (NM_005245.3:c.10957G>T). Finally, in a NLAPI subject who developed AMKL, and shared a P/LP variant in *FLG* with their sibling who developed HL (family #2), a non-shared rare P/LP variant was identified in exon 2 of *GATA1* (NM_002049.3:c.115G>T) (*Online Supplementary Table S5*), in which somatic mutations are known drivers of AMKL. Of note, this GATA1 variant had an allele fraction of 71.4% and was detected in the subject identified with trisomy 21 (subject #534; see above); thus, it is likely to be a somatic *GATA1* mutation that would be indicative of transient abnormal myelopoiesis (TAM), which occurs frequently in newborns with DS and is a precursor to AMKL in some cases.[20]

Table 1. Demographics of the 32 proband-sibling pairs, California Cancer Registry, 1989-2015.

	Overall N=64	Proband N=32	Affected sibling N=32
Self-reported race/ethnicity, N (%)			
Latino, all races	24 (37.5)	12 (37.5)	12 (37.5)
NLW	20 (31.3)	10 (31.3)	10 (31.3)
NLB	6 (9.4)	3 (9.4)	3 (9.4)
NLAPI	12 (18.8)	6 (18.8)	6 (18.8)
NLAIAN	2 (3.1)	1 (3.1)	1 (3.1)
Cancer site, N (%)			
Leukemias	27 (42.2)	12 (37.5)	15 (46.9%)
Lymphomas	17 (26.6)	9 (28.1)	8 (25.0)
Brain tumors	5 (7.8)	3 (9.4)	2 (6.2)
Neuroblastoma	1 (1.6)	1 (3.1)	0 (0)
Retinoblastoma	1 (1.6)	1 (3.1)	0 (0)
Renal tumors	1 (1.6)	1 (3.1)	0 (0)
Hepatic tumors	1 (1.6)	0 (0)	1 (3.1)
Bone tumors	1 (1.6)	0 (0)	1 (3.1)
Sarcomas	5 (7.8)	3 (9.4)	2 (6.2)
Germ cell tumors	3 (4.7)	2 (6.2)	1 (3.1)
Neoplasms and melanomas	2 (3.1)	0 (0)	2 (6.2)
Sex of child, N (%)			
Male	38 (59.4)	16 (50.0)	22 (68.8)
Female	26 (40.6)	16 (50.0)	10 (31.2)
Age in years, mean (SD)	9.75 (7.10)	6.22 (5.45)	13.3 (6.86)

N: number; NLW: non-Latino White; NLB: non-Latino Black; NLAPI: non-Latino Asian/Pacific Islander; NLAIAN: non-Latino American Indian/Alaskan Native; SD: Standard Deviation.

Ancestry of pathogenic/likely pathogenic germline variants

For the one LAT family with a shared sibling variant, the P/LP variant in *ATM* was shared on an SAS haplotype. For NLW families, the P/LP variants on *TP53* and *NOD2* shared EUR ancestry, which match their predicted dominant global ancestry. For one NLB family, the P/LP variant on *GATA2* shared AFR ancestry on local haplotypes and this matches their predicted dominant global ancestry. For NLAPI families, 2 pathogenic variants were classified as AMR and one (the novel *HABP2* variant) as EAS. For the one NLAIAN family, the P/LP variant on *SBF2* has shared local EUR ancestry, which matched their predicted dominant global ancestry (Figure 1, *Online Supplementary Table S3*).

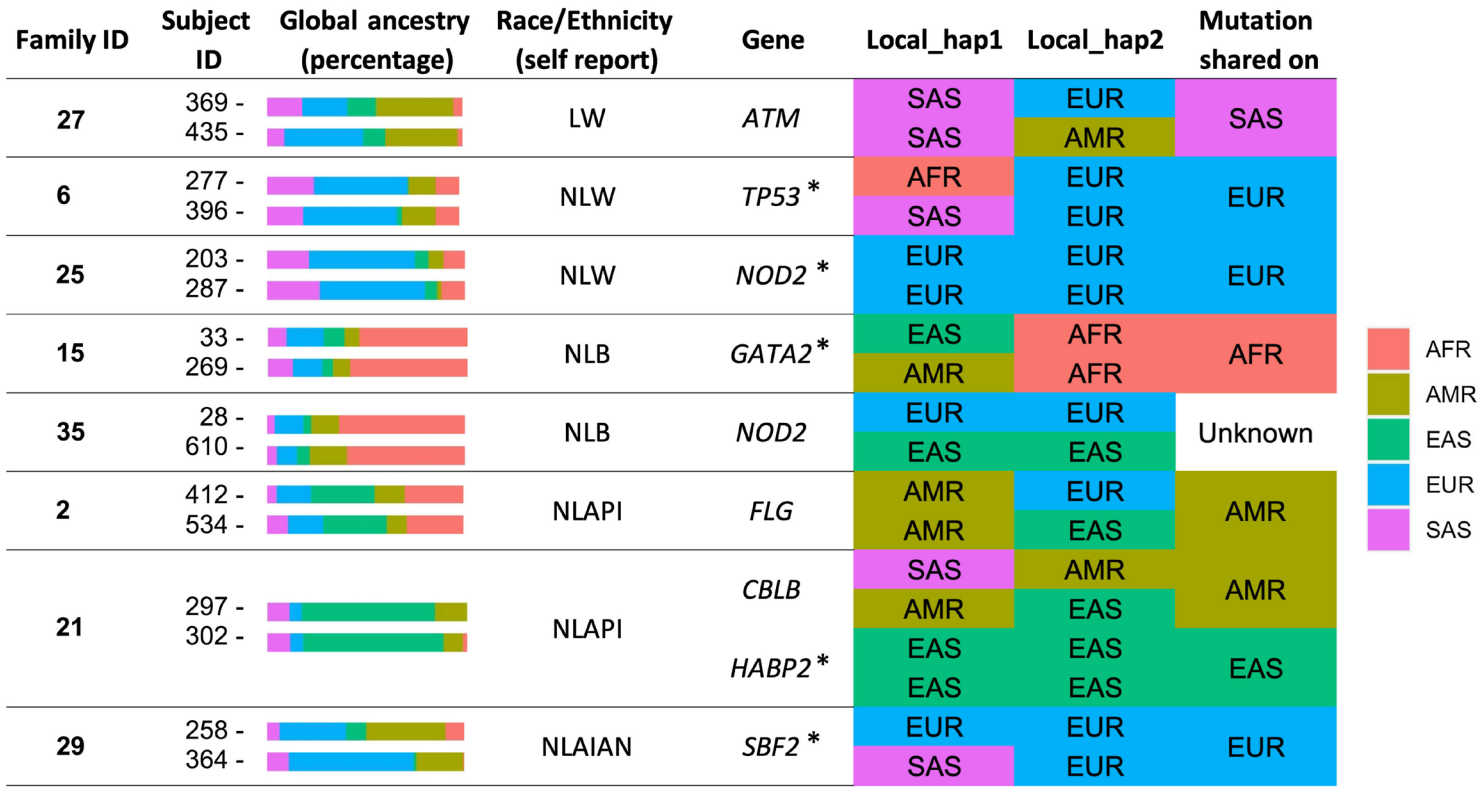

Figure 1. Predicted global ancestries of study subjects and local ancestries of putatively pathogenic variants, California Cancer Registry, 1989-2015. *Predicted local ancestry matches the predicted dominant global ancestry. LW: Latino White; NLW: non-Latino White; NLB: non-Latino Black; NLAPI: non-Latino Asian/Pacific Islander; NLAIAN: non-Latino American Indian/Alaskan Native; AFR: African; AMR: Admixed American; EAS: East Asian; SAS: South Asian; EUR: European.

Table 2. Distribution of rare variants shared by two siblings in a family, California Cancer Registry, 1989-2015.

	Pathogenic variants N=9	VUS N=105	Overall mutations N=113	N. of families N=32	VUS per family
Self-reported race/ethnicity, N (%)					
Latino, all races	1 (11)	41 (39)	44 (39)	12 (38)	3.2
NLW	2 (22)	21 (22)	24 (21)	10 (31)	2.2
NLB	2 (22)	10 (10)	12 (11)	3 (9)	3.3
NLAPI	2 (22)	27 (28)	31 (27)	6 (19)	4.7
NLAIAN	1 (11)	1 (1)	2 (2)	1 (3)	1.0
Category, N (%)					
Cancer	6 (73)	79 (68)	78 (69.0)	28 (58)	2.4
Hematologic	1 (7)	10 (11)	12 (10.6)	11 (23)	1.0
Immunologic	1 (13)	9 (9)	11 (9.7)	8 (17)	1.1
Other	0 (0)	2 (2)	1 (0.9)	1 (2)	1.0
Mutation class, N (%)					
Frameshift	6 (67)	-	6 (5)	6 (14)	0.0
Missense	-	105 (97)	101 (89)	30 (71)	3.2
Nonsense	3 (33)	0 (0)	3 (3)	3 (7)	0.3
Protein deletion	-	2 (2)	2 (2)	2 (5)	1.0
Splice	-	-	1 (1)	1 (2)	0.0

VUS: variants of uncertain significance; NLW: non-Latino White; NLB: non-Latino Black; NLAPI: non-Latino Asian/Pacific Islander; NLAIAN: non-Latino American Indian/Alaskan Native.

Discussion

This is the first study to our knowledge using purely population-based, no patient contact resources to examine genetic causes of family-based cancer clustering. We demonstrate that deleterious variants shared between family members contribute to early-onset hematologic cancers and that these can be revealed using California's linked birth and cancer registries and neonatal blood spot Biobank. This establishes the utility of these population-based resources to study familial cancer predisposition successfully, as well as to identify germline inherited risk alleles among varied ancestral groups. The profile of germline P/LP variants across ancestral/ethnic groups share similarities as well as distinctive characteristics. Consistent with previous findings, we note that individuals with familial early-onset hematologic cancers harbor deleterious germline variants in *TP53, GATA2*, and *ATM*.[9,21] Pathogenic variants in *TP53* have been associated with many hematologic cancers including lymphoblastic,[22] myeloid leukemias,[23] and lymphomas.[24-26] Deleterious germline variants in *GATA2* have been associated with myeloid malignancies,[27,28] and variants in *ATM* have been associated with T-cell prolymphocytic leukemia,[29] mantle cell lymphoma,[30] and gliomas.[31] The non-shared *SMARCA4* germline P/LP variant that we identified in a subject with teratoma is consistent with previous reports that have described germline mutations in *SMARCA4* for teratomas.[32,33]

Some P/LP variants exhibit novelty. The shared SBF2 in one NLAIAN family is a novel discovery in childhood cancers. *SBF2* is associated with cancer by a newly identified long non-coding RNA, SBF2-AS1. SBF2-AS1 was initially characterized in non-small cell lung cancer,[34] and has recently been reported to be over-expressed in multiple adulthood cancers in an East Asian population.[35-46] P/LP variants in *NOD2* is also a novel discovery in childhood cancers, and, intriguingly, one variant was found in 2 siblings who both developed HL. *NOD2* is a gene that is involved in immune response,[47] and has been associated with colorectal cancer.[48] In addition, we also reported a shared *FLG* mutation in association with childhood hematologic cancers. Somatic mutations of this gene have been reported to be associated with autoimmune diseases.[49] A *HABP2* mutation was shown to be shared between siblings with malignant large-B-cell lymphoma and neuroblastoma. *HABP2* encodes a serine protease, and an inactivating mutational variant (G534E) distinct from the one found here was previously linked to extramedullary thyroid neoplasia.[50] The nonsense mutation found here in this gene (C290*) has not been reported previously and likely represents a private familial mutation.

There are several strengths and limitations of this study. A major strength is the linkage of population-based cancer registries to identify subjects for sequencing. Thus, we have established a novel perspective on genetic predisposition that drives the excessive familial risk of early-onset hematologic cancers without selection or recruitment bias that may affect clinic or referral-based studies. We found P/LP alleles in about a quarter (25%) of families, as well as many suspect VUS alleles in addition, and an additional 7 families (22%) that have a P/LP mutation in one child only. This compares with the approximately 5-10% frequency of such alleles in sample series chosen without regards to family history.[3-6] A study that examined predisposition in the context of multiple sibling myeloid cancers in families using anecdotal clinical referral recruitment of families and liberal mutation identification criteria found candidate mutations in 83 of 86 families.[51] While we also similarly found VUS and P/LP mutations in nearly every subject, we emphasize the reporting of highly curated L/LP alleles, which in our 64 subjects yielded 23 (36%) mutations. Given the large size of our base population and definition of "cancer families" as those with a minimum of only 2 cases, it is likely that some families will be afflicted by multiple cancers by chance without predisposing alleles or be influenced via familial sharing of an environmental exposure. Still, our 36% yield compares with a 4.4% yield in an assessment of leukemia-associated P/LP mutations in a large study of sporadic patients,[4] attesting to the power of population-based recruitment in the current investigation.

Benefiting from the highly diverse population in California, we are the first research group that has assessed the variation in genetic predisposition in association with familial hematologic cancer risk in multiple ancestral/ethnic groups over a defined population, appraising cancer predisposition in a selection-bias free, consent-bias free population. However, limited by the length of time in data collection and the rarity of childhood cancers, we have only identified a selection of mutations that are unique to an ancestral/ethnic group. In addition, we have no way to evaluate or confirm the impact of non-shared P/LP alleles inherited by chance by those siblings that did not share a P/LP allele. Also, limited to analysis of SNV and indels, we did not assess variation in copy number or epigenetic alterations that may be potentially pathogenic.

Cancer risk is increased by both genetic and environmental factors. Family members are generally exposed to the same environments and therefore those in-common environments may contribute to the observed familial cancer clustering. To understand such clustering better, concomitant assessments of environmental factors in coordination with germline genetics should be considered for future studies. Such analyses will help to establish the role of strong cancer predisposition variants more definitively among different ancestral/ethnic groups, and whether such mutations harbor varied penetrance in the context of different ancestral backgrounds and environments. This type of evaluation is increasingly critical in the intermixed population of California and other world regions, and has profound implications for family genetic counseling in the context of improved cancer patient survival.

Disclosures

No conflicts of interest to disclose.

Contributions

QF and KX performed primary data analysis, with help from SL. MS performed manual variant classifications. AL, LAG and JLW conceived the study and acquired funding. AJdS and JLW supervised statistical analysis, with help from MS and LAG. QF wrote the first draft, and JLW, LAG, and AJdS completed the writing team. All authors read and approved the final draft.

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Data-sharing statement

Sharing of raw and processed whole exome sequencing data from California Biobank specimens is restricted by California state statutory laws and IRB (see Online Supplementary Appendix for further details). Results from specific genes or regions may be requested from wiemels@usc.edu.

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