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RESEARCH ARTICLE

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Extended familial risk of suicide death is associated with younger age at death and elevated polygenic risk of suicide

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Abstract

Suicide accounts for >800,000 deaths annually worldwide; prevention is an urgent public health issue. Identification of risk factors remains challenging due to complexity and heterogeneity. The study of suicide deaths with increased extended familial risk provides an avenue to reduce etiological heterogeneity and explore traits associated with increased genetic liability. Using extensive genealogical records, we identified high-risk families where distant relatedness of suicides implicates genetic risk. We compared phenotypic and polygenic risk score (PRS) data between suicides in high-risk extended families (high familial risk (HFR), $n = 1{,}634$), suicides linked to genealogical data not in any high-risk families (low familial risk (LFR), $n = 147$), and suicides not linked to genealogical data with unknown familial risk (UFR, $n = 1{,}865$). HFR suicides were associated with lower age at death (mean = 39.34 years), more suicide attempts, and more PTSD and trauma diagnoses. For PRS tests, we included only suicides with >90% European ancestry and adjusted for residual ancestry effects. HFR suicides showed markedly higher PRS of suicide death (calculated using cross-validation), supporting specific elevation of genetic risk of suicide in this subgroup, and also showed increased PRS of PTSD, suicide attempt, and risk taking. LFR suicides were substantially older at death (mean = 49.10 years), had fewer psychiatric diagnoses of depression and pain, and significantly lower PRS of depression. Results suggest extended familiality and trauma/PTSD may provide specificity in identifying individuals at genetic risk for suicide death, especially among younger ages, and that LFR of suicide warrants further study regarding the contribution of demographic and medical risks.

KEYWORDS
familial risk, polygenic risk, suicide

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1 | INTRODUCTION

Over 48,000 individuals die by suicide in the United States every year (WHO, n.d.; Statistics|Suicide|Violence Prevention|Injury Center, n.d.). Prediction and prevention has become a high priority for public health. Identification of risk factors remains challenging due to the complexity of suicide risk; however, genetic factors comprise one important aspect of risk. Estimates of heritability for both suicide behaviors and suicide death from multiple studies are approximately 50% (McGuffin, Marusic, & Farmer, 2001; O'Reilly et al., 2020; Pederson & Fiske, 2010; Roy & Segal, 2001; Voracek & Loibl, 2007), and genetic studies of suicide behaviors are beginning to reveal promising findings (Docherty et al., 2020; Mullins et al., 2019; Otsuka et al., 2019; Ruderfer et al., 2019; Sokolowski, Wasserman, & Wasserman, 2014; Strawbridge et al., 2019). However, questions remain regarding dependence of suicide risk on co-occurring psychiatric diagnoses and differences in risks among the suicidal outcomes of attempt and death (Campos et al., 2020; Docherty et al., 2020; Erlangsen et al., 2018; Levey et al., 2019; Mullins et al., 2019). In particular, more work is required to understand specific genetic risks associated with suicide death, where risk prediction remains particularly challenging (Franklin et al., 2017). Suicide attempts, which occur at 10–25 times the rate of suicide deaths (Bostwick, Pabbati, Geske, & McKean, 2016), are currently the strongest predictor of suicide death (Bostwick et al., 2016; Campos et al., 2020; Docherty et al., 2020; Erlangsen et al., 2018; Franklin et al., 2017; Harris & Barraclough, 1997; Levey et al., 2019; Mullins et al., 2019, 2022; Otsuka et al., 2019; Owens, Horrocks, & House, 2002; Strawbridge et al., 2019), but a highly imperfect predictor, as fewer than 8% of individuals with a prior attempt will go on to die by suicide (Carroll, Metcalfe, & Gunnell, 2014; Harris & Barraclough, 1997; Owens et al., 2002). We urgently need to improve our knowledge of risk of this most extreme outcome.

In this analysis, we make use of unique deep genealogical data to begin to address these important etiological questions. The Utah Suicide Genetic Risk Study (USGRS) has a large collection of biosamples from suicide deaths (Coon et al., 2020; Docherty et al., 2020), with genotyping and health records data currently available for this study from 3,646 of these cases. The study benefits from population-wide ascertainment, and is therefore not limited to cases within particular psychiatric diagnoses, allowing for broader study of genetic risk that crosscut diagnoses. The USGRS additionally has access to deep genealogical data dating back over two centuries that allows for the identification of suicides with significantly elevated extended familial risk well beyond information available from clinical interviews. Because this familial risk comes from distantly related suicide deaths who shared little to no common familial environment, suicides in these high-risk families likely have enhanced familial genetic risk. This study offers an opportunity to study demographic, diagnostic, and genetic characteristics of these HFR suicides, and to compare them to suicides without significant extended familial risk.

Adding to the extensive demographic and clinical data in our resource, genome-wide genotyping allows for characterization of polygenic risks by applying available summary results from external published genome-wide association studies (GWAS) for psychiatric and medical diagnoses, and behavioral traits (Levey et al., 2019). The resulting polygenic risk scores (PRS), calculated using genome-wide genotyping data on USGRS suicide deaths, represent distributions of underlying polygenic genetic risks of these diagnoses and behaviors. For example, effect sizes of single nucleotide polymorphisms (SNPs) across the genome have been reported in a large case–control genome-wide association study of PTSD (Nievergelt et al., 2019). PRS for PTSD for an individual in our study is then calculated as the summation of each SNP for that case multiplied by the effect size of that SNP in the discovery PTSD study. Importantly, PRS may reveal genetic risk of adult onset diagnoses in youth not yet through the age of risk, or genetic risk of disorders requiring exposure (such as PTSD) even if that exposure has not occurred. For certain traits such as obesity, where environmental factors play a strong role, PRS may also more accurately reflect genetic liability.

In this study, we identify, then characterize HFR suicides and compare them to those with low and those with UFR. Polygenic risk scores of suicide attempt and suicide death (calculated from our data using cross-validation and controlling for extended family relatedness) allow a direct test of our hypothesis that the HFR suicides may have enhanced suicide-specific genetic risk compared to low- and unknown-familial-risk (UFR) suicides. Additional demographic, diagnostic, and co-occurring trait PRS allowed us to explore the hypothesis that familial suicide may also be associated with clinical and genetic risks of other diagnoses and traits. Finally, our data also allowed us to determine demographic, clinical, and genetic associations with suicides showing LFR.

2 | METHODS

2.1 | Samples and phenotypes

The USGRS benefits from more than two decades of unprecedented close collaboration with the Utah Department of Health's centralized Office of the Medical Examiner (OME). Suicide status is made by the OME following detailed investigation of the scene and circumstances

of the death, and is given conservatively due to its impact on survivors. High-quality DNA is extracted and processed as previously described (Coon et al., 2020). Identifiers from cases are used to link each death to data within the Utah Population Database (UPDB; https://uofuhealth.utah.edu/huntsman/utah-population-database/) using secure computer servers. The UPDB is a state-wide database that contains over 27 million data records on over 12 million individuals, including demographics, two decades of health records data, and deep genealogical data. After linking, identifiers are stripped before data are given to the research team to protect privacy and confidentiality. This study is approved by Institutional Review Boards from the University of Utah, Intermountain Healthcare, and the Utah Department of Health. For this study, we used a subset of 3,646 deaths with both genotyping and electronic health records (EHRs) data.

2.2 | Utah genealogical data and ascertainment of high-risk families

Utah genealogical records include 1,916,649 records and date back to the late 1700s. For this study, an extended family was defined as high risk when the observed number of suicide deaths in the family was significantly elevated compared to the expected familial incidence using the Familial Standardized Incidence Ratio statistic (FSIR; Boucher & Kerber, 2001; Kerber, 1995). The FSIR is a familial risk ratio, calculated by comparing the incidence of suicides in each extended family (given its size and structure) to the expected incidence determined by the statewide distribution for suicide stratified by sex and age. It is designed to be used at the level of the family, and is most robust when applied to families of at least 100 family members, particularly when applied to a rare trait such as suicide death. Utah death certificates dating back to 1904 include >20,000 suicide deaths, resulting in the identification of 946 Utah extended families with at least 100 members who were between 4 and 11 generations, and met FSIR significance of $p \leq 0.01$. There was an average of ninth-degree relatedness between pairs of familial suicide deaths (see Figure 1a for examples of high-risk extended families). The distant relationships among cases in these families indicate they likely share little familial environment, suggesting that the significant FSIR is due primarily to increased familial genetic risk.

2.3 | Use of familial risk as a discrete trait

Due to the complexity of genealogical data, it is not uncommon to observe suicide deaths related through multiple ancestry lines to more than one high-risk extended family. Extended families can also exhibit varying degree of overlap (see Figure 1b for an example). Because of this complexity, we chose to use high-risk familial membership as a discrete variable for the purposes of this study. Therefore, suicide deaths linked to one or more high-risk family were defined as HFR suicide deaths. Using 106,325 Utah population controls, matched by age and sex to these suicide deaths, we also ascertained 47,0457 Utah control families with >100 members and between 4 and 11 generations. This ascertainment of control families allowed estimation of the proportion of families at high risk for suicide death.

2.4 | Definition of low and UFR

Suicide deaths with genealogical data in the UPDB, defined as having at least 100 relatives in the genealogical records (as was done for the high-risk family definition), but not linking to any of the 946 high-risk families, were defined as LFR suicide deaths for the purposes of this study. Suicide deaths without sufficient genealogical data (fewer than 100 relatives in the genealogical records) were defined as UFR cases. Familial risk group definitions were made blind to any demographic, diagnostic, or genetic data. We hypothesized that UFR suicides may represent more recent in-migration to Utah where individuals do not link to the genealogical data.

2.5 | EHR linking

Suicide deaths were securely linked to diagnostic EHR codes from three sources by UPDB personnel. These sources included data from all statewide inpatient and ambulatory care encounters from the Utah State Health Department, and data from outpatient encounters from the largest two clinical data providers in the state (University of Utah Healthcare and Intermountain Healthcare), representing ~85% of the state's outpatient encounters. The inpatient and outpatient International Classification of Diseases (ICD-9 and ICD-10) (https://www.cdc.gov/nchs/icd/icd9.htm; https://www.cdc.gov/nchs/icd/icd10cm.htm) codes were curated within the UPDB to eliminate duplication. Diagnoses within 1 month prior to suicide death were excluded to eliminate diagnoses associated with the final suicide event rather than those reflecting prior psychiatric/medical co-morbidities. For efficient characterization of diagnoses, we collapsed the diagnostic data into interpretable categories using hierarchical classification derived through expert clinical adjudication (Drs. Keeshin, Crowell, Docherty, and Monson). For this study, we included diagnostic categories with prior evidence for association with suicide risk. Suicide attempt codes associated with the actual suicide death were not considered as part of the category of prior suicide attempt. The ICD-9 and ICD-10 diagnoses within each category are listed in Table S1.

2.6 | Genotyping and quality control

A total of 3,704 Utah suicides collected between 1998 and 2018, linked to EHR data and also had genotyping data from the Illumina PsychArray platform (https://www.illumina.com/techniques/microarrays/array-data-analysis-experimentaldesign/genomestudio.html). Quality control of genotyping data was performed as previously described (Docherty et al., 2020). Because polygenic risk discovery statistics are available

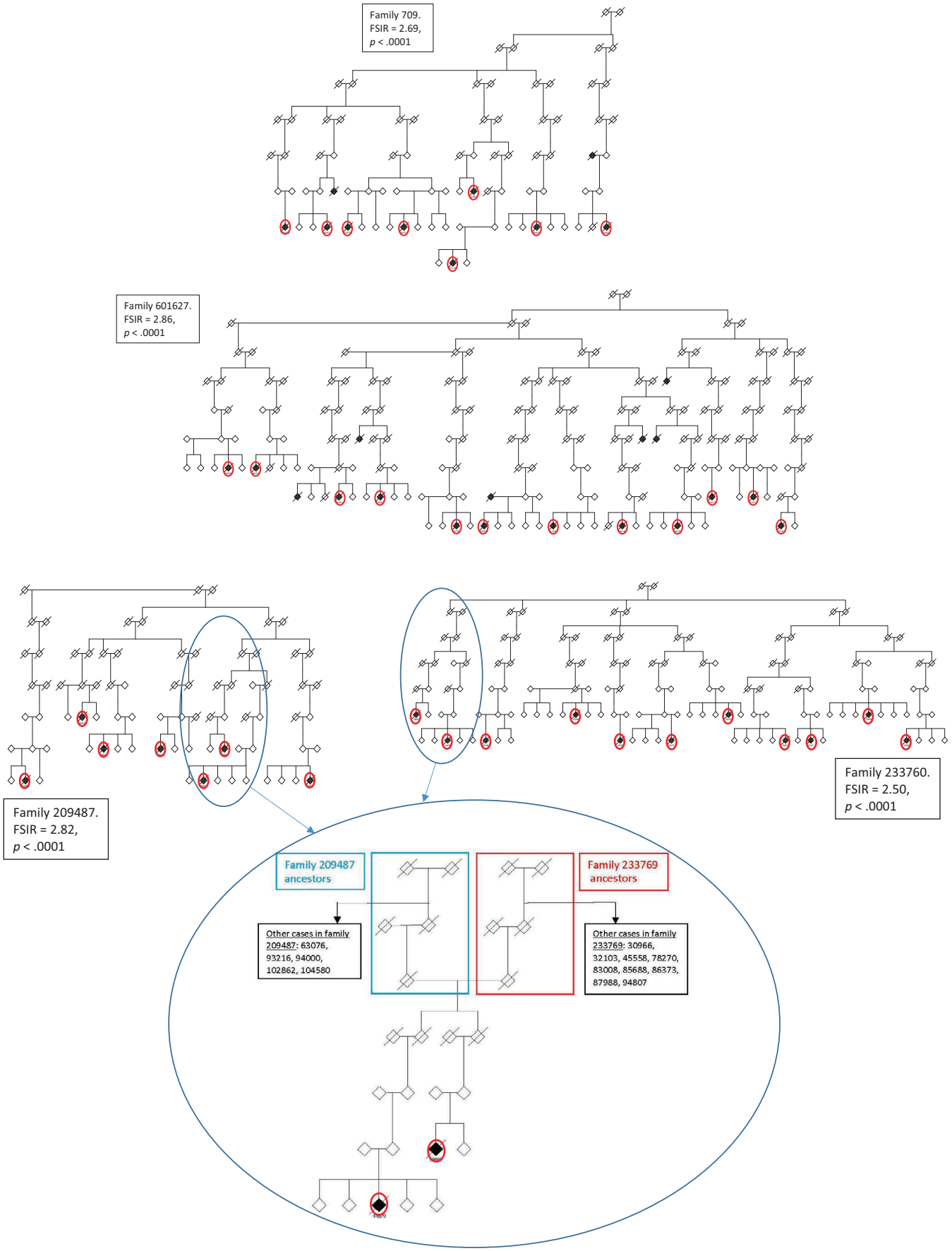

FIGURE 1 Legend on next page.

primarily from studies of individuals of European descent, the PRS analyses were only performed for suicide deaths in our sample of >90% European descent. For the present study, we employed ancestry derived from comparisons of our genotype data to reference data computed for our previously published genome-wide association study (Docherty et al., 2020). In addition, while most suicides in our data resource are not closely related, relatedness was verified using genotype data (Purcell et al., 2007). For close relative pairs (pi-hat ≥0.125), one member of each pair ($N = 58$) was randomly omitted, leaving 3,646 suicides for subsequent analyses.

2.7 | Polygenic risk scoring of diagnoses and behavioral traits

PRS for the phenotypes best corresponding to the diagnostic categories was computed using the most recent available external discovery GWAS studies (Zheng et al., 2017). PRSice 2.0 (Euesden, Lewis, & O'Reilly, 2014) was used to calculate individual PRS diagnoses and traits most closely associated with the clinical diagnostic categories. A PRS is essentially a weighted sum score, where a score for an individual in the target sample is calculated by the summation of each SNP multiplied by the effect size of that SNP in the discovery GWAS. PRSs were calculated using all data in the discovery GWAS studies, rather than imposing multiple *p*-value thresholds. While performance of the PRS may be somewhat reduced by using all data (So & Sham, 2017), we show that the derived PRS in the present analysis is relatively robust to this *p*-value threshold choice; any effect on results is likely to be conservative (see Figure S1). Additionally, using all data avoids the penalty of multiple testing across many thresholds.

Assessment of PRS for suicide death was derived from our Utah GWAS (Docherty et al., 2020) using summary statistics from a 10-fold cross-validation procedure as follows. The sample was divided into 10 equal folds. For each set of nine folds, a GWAS accounting for ancestry was performed, then results were used to create a suicide death PRS for the 10 fold. Relatedness was also strictly controlled. In addition to removing all closely related (pi-hat ≥0.125) suicides as noted above, we additionally ensured that no suicides with more distant extended familial relationships were included within any of the 10 folds. This cross-validation procedure was done 10 times, ensuring that for every sample, its polygenic score of suicide death was based on a GWAS that did not include that sample, and additionally did not include any distantly related samples.

2.8 | Comparisons among HFR, LFR, and UFR suicide deaths

We note that tests between HFR and LFR groups represent the most precise comparison in our study because all cases in these two groups linked to genealogical records and familial risk status was therefore known. However, due to the small number of LFR cases, HFR and LFR groups were additionally compared to the larger UFR group where familial risk was unknown, as a more statistically powerful comparison but not informed by direct knowledge of extended familial risk. For all variable domains (demographic, clinical, and polygenic risk data), pairwise comparisons were used to explicitly test directional effects anticipated in the HFR and LFR groups. For all analyses, nominal significance is reported for a false discovery rates (FDR) of <0.05 and <0.10 across all comparisons.

2.8.1 | Demographic data

Logistic regression models were used to compare across HFR versus UFR, LFR versus UFR, and HFR versus LFR for sex effects, effects of age at death (controlling for sex), genotype-derived European ancestry (controlling for sex and age at death), and overall number of psychiatric and clinical diagnoses (controlling for sex and age at death). Method of death was coded as non-violent for deaths due to poisoning and violent for deaths due to firearms, hanging, cutting, jumping from heights, drowning, and other more extreme violent means (Stenbacka & Jokinen, 2015).

2.8.2 | Clinical data

Differences were examined in the frequencies of diagnoses within the 13 aggregated diagnostic categories among HFR, LFR, and UFR risk groups. These tests were done using pairwise logistic regression, with number of diagnoses within the category square root transformed to improve distributional properties, and with additional covariates of age at death and sex. The modeled outcome was familial risk group status.

2.8.3 | Polygenic risk data

Differences in PRS of 14 traits/diagnoses were also tested using pairwise logistic regression with familial risk group again as the

FIGURE 1 (a) Examples of Utah family clusters at high risk for suicide death. Shaded symbols are suicide deaths; cases circled in red have genotyping data. Gender is disguised and sibship order is randomized to protect family privacy. For determining high-risk family status, we used suicide status dating to 1904 from Utah death certificates. For the 946 high-risk Utah family clusters with >100 family members and FSIR statistic meeting *p*-value for risk ≤0.01, the average pairwise relatedness among suicide cases was ninth degree. DNA samples from suicide deaths in this study were collected between 1998 and 2018. (b) An example of cases linked to more than one extended high-risk family, not an uncommon occurrence in the complex genealogical data

independent variable. Traits/diagnoses were selected to approximately match clinical diagnostic categories, and where the discovery study included at least 10,000 individuals (see Table S2 for references of discovery studies). As noted above, in these models, we included only suicides with ≥90% genotype-derived European ancestry from our published GWAS study. This restriction reduced sample sizes to 1,551 HFR, 137 LFR, and 1,462 UFR suicides. Models again included covariate effects of age at death and sex, and additionally adjusted for 10 additional ancestry principal components to account for any residual ancestry effects above and beyond the restriction imposed by including only 90% European samples. Height was examined as a PRS control variable. Biometrical traits are sensitive to ancestry effects; lack of observed significance for height therefore indicates sufficient correction for ancestry effects (Bitarello & Mathieson, 2020).

2.8.4 | Post hoc analyses to explore readily available factors approximating HFR status

Extended genealogical data are not common. Indeed, in the absence of deep, detailed genealogical records, familial risk beyond first cousin relatedness is often unknown, and distant relatedness is not reliably detectable in genetic data. In addition, although PRS of suicide death may help identify genetic liability, genetic data also may not always be available. More importantly, clinical application of a PRS for suicide death, while informative for tests between groups, would be poorly predictive at the individual level, especially in the absence of knowledge of complex environmental and social individual risks (Docherty et al., 2021; Kious et al., 2021). Therefore, we designed post hoc tests to determine the extent to which more easily measured traits could help identify those at elevated risk for suicide death. We selected on the demographic and clinical variables from our results completely independent of HFR status to simulate a scenario where HFR status was unknown. The results give information regarding the possibility that these other characteristics could provide an adequate proxy to identify one or more subgroups at higher genetic risk. For young age at death, we tested quantitative age, and also selected suicides (independent of familial status) that were above vs. below the overall mean age at death in Utah suicides (41.22) and applied logistic regression. This dichotomous test allowed for clear visualization of directions of effect. For clinical variables, we tested for presence versus absence of the clinical diagnoses in that category.

3 | RESULTS

Linkage of suicides to genealogical data resulted in 1,634 HFR suicide deaths, 147 low-familial-risk (LFR) suicide deaths, and 1,865 UFR suicide deaths. The HFR suicides were linked to one or more of the 946 defined extended high-risk families of 4–11 generations and >100 family members with FSIR p values ranging from 0.01 to <.0001. The 106,325 age- and sex-matched Utah controls resulted in 47,057 Utah families of >100 family members between 4 and 11 generations. The 946 high-risk suicide families therefore represent ~2% of families of this size in the UPDB. Of the 1,781 suicide deaths linking to the genealogical data, the vast majority (1,634/1,781 = 91.75%) linked to a high-risk family.

3.1 | Demographic data

Table 1 presents descriptive differences between HFR, LFR, and UFR suicide deaths, with a comparison to the overall characteristics of the combined groups. No significant sex ratio differences were found across the three groups. In contrast, the average age at death in HFR suicides (39.34 years) was significantly younger compared to UFR suicides (42.34 years) and to LFR suicides (49.10 years; both comparisons $p < .0001$). LFR suicides were also significantly older at death than UFR suicides ($p < .0001$). Ancestry was significantly more European for both the HFR and LFR suicides linked to genealogical data versus the UFR suicides of unknown familial status ($p < .0001$ and $p = .0009$, respectively). The HFR suicides were nominally more European than the LFR suicides ($p = .02$). While all suicides in this analysis had linked EHR codes, overall numbers of aggregated medical and psychiatric diagnostic codes revealed fewer codes in the LFR group compared to the HFR and UFR groups. The HFR and UFR were not significantly different from one another. No significant differences were found for percentage of violent death across any familial risk group comparison, adjusting for age and sex (data not shown).

3.2 | Clinical diagnoses

Table 2 shows the differences among HFR, LFR, and UFR suicides for clinical diagnoses aggregated over diagnostic categories, adjusted for age at death and sex. The table shows all nominally significant p values, and notes results meeting significance at false discovery rates (FDR) of <0.05 and 0.10. Among the psychiatric diagnosis domains, HFR compared to UFR suicides had nominally elevated evidence of prior suicide attempts (OR = 1.10, 95% CI = 1.01–1.20; $p = .025$) and nominally higher prevalence of accidental trauma and PTSD diagnostic codes (OR = 1.05; 95% CI = 1.01–1.09; $p = .025$). The trauma/PTSD association was still apparent when comparing HFR to LFR suicides. Depression diagnoses were lower in LFR compared to UFR suicides (OR = 0.82, 95% CI = 0.72–0.95; $p = .004$), and anxiety diagnoses were nominally lower (OR = 0.82, 95% CI = 0.70–0.95; $p = .02$). The associations with depression and anxiety persisted in the comparison of HFR to LFR suicides, driven by the low prevalence of these diagnoses in the LFR group.

Among diagnoses in the medical domain, comparisons of LFR to UFR suicide deaths showed lower prevalence of diagnoses in the pain (OR = 0.88, 95% CI = 0.81–0.97; $p = .004$), and nominal associations with sleep (OR = 0.80, 95% CI = 0.66–0.97; $p = .01$) and cardiovascular disease (CVD; OR = 0.90, 95% CI = 0.82–0.99; $p = .01$) categories, adjusted for effects of sex and age at death. Differences for pain and sleep diagnoses nominally persisted in the comparison of LFR to HFR suicides.

TABLE 1 Characteristics of high-familial-risk, low-familial-risk, and unknown-familial-risk suicide deaths

Characteristic	Percent or mean (SD)				Odds ratio (95% CI, *p*-value)		
	All groups ($n = 3,646$)	HFR suicides ($n = 1,634$)	LFR suicides ($n = 147$)	UFR suicides ($n = 1,865$)	HFR vs. UFR	LFR vs. UFR	HFR vs. LFR
% male	76.77%	77.05%	77.55%	76.46%	1.01 (0.85–1.19, NS)	1.01 (0.63–1.40, NS)	0.98 (0.69–1.53, NS)
Age at death[a]	41.22 (17.69)	39.34 (17.17)	49.10 (19.85)	42.25 (17.72)	**0.984 (0.98–0.99, <.0001)**[b]	**1.02 (1.01–1.03, <.0001)**[b]	**0.97 (0.96–0.98, <.0001)**[b]
European ancestry[c]	92.71 (18.06)	97.45 (6.65)	96.67 (9.29)	88.24 (23.48)	**1.06 (1.05–1.07, <.0001)**[b]	**1.03 (1.01–1.05, .0009)**[b]	1.02 (1.003–1.04, .02)
N psychiatric ICD codes[c]	17.21 (41.29)	17.29 (41.60)	10.27 (19.01)	17.69 (42.25)	**1.00 (0.99–0.03, NS)**	**0.93 (0.87–0.99, .02)**	**1.09 (1.02–1.17, <.0001)**
N medical ICD codes[c]	31.81 (66.49)	30.39 (62.59)	26.68 (44.97)	33.42 (71.06)	1.00 (0.99–1.03, NS)	**0.94 (0.89–0.99, .01)**[d]	**1.07 (1.02–1.13, <.0001)**[b]

Note: All results with at least nominally significant *p* values are in bold type.
[a]Adjusted for sex.
[b]Indicates significance at a false discovery rate (FDR) of <0.05 across all pairwise tests.
[c]Adjusted for sex and age at death.
[d]Indicates significance at a false discovery rate (FDR) of <0.10 across all pairwise tests.

3.3 | Polygenic risks

Table 3 presents PRS comparisons for psychiatric and medical traits matching the studied clinical diagnoses. The subset of suicides with ≥90% European ancestry included in these tests resulted in these numbers of cases: 1,551 HFR, 137 LFR, and 1,462 UFR. Analyses were adjusted for age at death, sex, and 10 additional residual ancestry principal components. The table presents all nominally significant *p* values, and highlights those significant at false discovery rates (FDR) of 0.05 and 0.10. A secondary test including the 13.6% of our sample with ancestries <90% European and adjusting for 20 rather than 10 ancestry principal components did not differ substantively from these results in terms of patterns and approximate magnitude of significance (data not shown). Nonsignificant results for height (a variable highly affected by ancestry effects), which was tested as a control trait, indicate adequate adjustment for ancestry effects. While we computed results using all data in the discovery GWAS, results across 1,000 *p*-value thresholds are shown in Figure S1, demonstrating robustness to this analysis decision.

Notable results in the comparisons of HFR to UFR suicides include the strong association with polygenic risk of suicide death (OR = 3.10, 95% CI = 2.57–3.73; $p < .0001$), and an association with PTSD (OR = 1.20, 95% CI = 1.06–1.37; $p = .004$), in addition to suggestive associations with suicide attempt (OR = 1.13, 95% CI = 1.03–1.23; $p = .01$) and risk taking (OR = 1.10, 95% CI = 1.01–1.19; $p = .02$). HFR was also nominally associated with lower schizophrenia (OR = 0.84, 95% CI = 0.71–0.98; $p = .03$). The LFR comparison to UFR suicides showed a significant association with lower PRS of major depressive disorder (MDD; OR = 0.41, 95% CI = 0.20–0.71; $p = .001$). The direct comparison of HFR and LFR suicides, although diminished in statistical power, mirrored the results of higher PRS for suicide death and PTSD in the HFR group, and lower PRS for MDD in the LFR group.

3.4 | Post hoc analyses

Tests were done stratifying on the easily obtained demographic or clinical variables found to be significantly increased in HFR suicides: younger age at death (age < mean age of 41.22 years); presence of accidental trauma and/or PTSD diagnoses; and presence of the rarer outcome of documented prior suicide attempts. As a comparison, we also stratified by presence of depression diagnoses, a clinical variable not associated with HFR in our analyses, but commonly associated with suicidal behavior in the literature. For tests of polygenic risk scores, we again retained only those suicides with >90% European ancestries.

Diagnostic post hoc results (Table S3) showed expected increased prevalence of age-related diagnoses when stratified by young age at death (fewer diagnoses of cancer, cardiovascular disease, obesity, and pain in younger suicides), but no differences for psychiatric diagnoses. General linear models testing quantitative age at death produced results substantively unchanged from those in Table S3 (data not

TABLE 2 Differences in clinical diagnoses among high-familial-risk (HFR), low-familial-risk (LFR), and unknown-familial-risk suicide deaths

Mean *N* of diagnoses (*SD*)					Odds ratio (95% CI, *p*-value)[a]		
Diagnostic category	All suicides ($n = 3,646$)	HFR suicides ($n = 1,634$)	LFR suicides ($n = 147$)	UFR suicides ($n = 1,865$)	HFR vs. UFR	LFR vs. UFR	HFR vs. LFR
Suicide attempts	0.72 (2.62)	0.79 (2.67)	0.48 (1.42)	0.67 (2.65)	**1.10 (1.01–1.20, .025)**	0.96 (0.74–1.22, NS)	1.13 (0.88–1.45, NS)
Depression	3.45 (8.60)	3.47 (8.70)	1.93 (4.11)	3.55 (8.76)	1.02 (0.97–1.06, NS)	**0.82 (0.72–0.95, .004)**[b]	**1.23 (1.06–1.42, .005)**[c]
Anxiety	2.24 (6.30)	2.20 (6.51)	1.37 (3.87)	2.35 (6.27)	0.99 (0.94–1.05, NS)	**0.82 (0.70–0.97, .02)**	**1.22 (1.03–1.45, .01)**
Accidental trauma + PTSD	5.17 (10.45)	5.43 (10.04)	3.83 (6.43)	5.06 (**11**.03)	**1.05 (1.01–1.09, .025)**	0.92 (0.83–1.03, NS)	**1.14 (1.02–1.29, .02)**
Substance use disorders[d]	3.44 (12.07)	3.47 (12.02)	2.03 (5.12)	3.51 (12.49)	1.01 (0.97–1.06, NS)	0.90 (0.79–1.02, NS)	1.14 (1.0–1.30, NS)
Bipolar disorder	0.93 (4.79)	0.99 (5.06)	0.54 (2.67)	0.92 (4.67)	1.03 (0.96–1.11, NS)	0.92 (0.74–1.14,NS)	1.09 (0.87–1.36, NS)
Impulsivity	0.36 (1.98)	0.37 (1.99)	0.14 (0.69)	0.36 (2.04)	1.004 (0.90–1.13, NS)	0.84 (0.57–1.24, NS)	1.18 (0.78–1.80, NS)
Psychosis	0.19 (1.01)	0.21 (1.02)	0.07 (0.32)	0.19 (1.03)	1.09 (0.93–1.27, NS)	0.65 (0.36–1.16, NS)	1.72 (0.94–3.14, NS)
Pain	9.02 (21.93)	8.92 (21.01)	6.57 (12.81)	9.31 (23.25)	1.01 (0.98–1.05, NS)	**0.88 (0.81–0.97, .004)**[b]	**1.12 (1.03–1.23, .01)**
Sleep	1.46 (6.22)	1.40 (5.61)	1.02 (5.03)	1.55 (6.78)	1.00 (0.94–1.07, NS)	**0.80 (0.66–0.97, .01)**	**1.23 (1.01–1.50, .04)**
Cancer	0.62 (5.50)	0.45 (3.62)	0.42 (1.67)	0.78 (6.89)	0.95 (0.87–1.04, NS)	0.87 (0.68–1.10, NS)	1.08 (0.84–1.39, NS)
CVD	6.39 (21.01)	5.53 (18.90)	5.82 (13.66)	7.19 (23.11)	0.99 (0.95–1.02, NS)	**0.90 (0.82–0.99, .01)**	1.09 (1.00–1.20, NS)
Obesity	2.09 (9.02)	1.19 (7.54)	2.01 (8.01)	2.24 (10.21)	1.04 (0.98–1.09, NS)	0.94 (0.83–1.07, NS)	1.10 (0.96–1.27, NS)

Note: Diagnostic codes in each category are presented in Table S1. In the logistic regressions, covariate effects of sex and age at death are included, and the outcome events modeled are as follows: HFR status in the HFR versus UFR model; LFR status in the LFR versus UFR model; HFR status in the HFR versus LFR model. All results with at least nominally significant *p* values are in bold type. Raw means are presented in the table; for analysis, Ns of diagnoses within each category were square root transformed.

[a]Tests were adjusted for sex and age at death.

[b]Indicates significance at a false discovery rate (FDR) of <0.05 across all pairwise tests.

[c]Indicates significance at a false discovery rate (FDR) of <0.10 across all pairwise tests.

[d]Includes both alcohol and drug use disorders.

TABLE 3 Differences in polygenic risk scores of high-familial-risk, low-familial-risk, and unknown-familial-risk suicide deaths

Polygenic risk score	HFR (n = 1,551) vs. UFR (n = 1,462): OR (95% CI; p-value)	LFR (n = 137) vs. UFR (n = 1,462): OR (95% CI; p-value)	HFR (n = 1,551) vs. LFR (137): OR (95% CI; p-value)
Suicide death	**3.10 (2.57–3.73; <.0001)**[a]	1.38 (0.90–2.13; NS)	**2.33 (1.51–3.61; .0001)**[a]
Suicide attempt	**1.13 (1.03–1.23; .01)**[b]	1.23 (0.99–1.54; NS)	0.92 (0.74–1.15; NS)
MDD	0.94 (0.75–1.18; NS)	**0.41 (0.20–0.71; .001)**[a]	**2.38 (1.35–4.21; .003)**[a]
Anxiety	0.98 (0.92–1.06; NS)	0.88 (0.74–1.06; NS)	1.13 (0.95–1.35; NS)
PTSD	**1.20 (1.06–1.37; .004)**[a]	0.95 (0.70–1.30; NS)	**1.40 (1.02–1.90; .04)**
ADHD	0.96 (0.89–1.03; NS)	0.89 (0.75–1.06; NS)	1.09 (0.92–1.30; NS)
Bipolar	0.96 (0.78–1.19; NS)	0.86 (0.52–1.42; NS)	1.06 (0.64–1.75; NS)
Schizophrenia	**0.84 (0.71–0.98; .03)**	0.76 (0.52–1.11; NS)	1.08 (0.73–1.61; NS)
Risk taking	**1.10 (1.01–1.19; .02)**	1.05 (0.98–1.20; NS)	1.04 (0.86–1.26; NS)
Drinks per week	1.02 (0.94–1.10; NS)	1.18 (0.97–1.43; NS)	0.90 (0.74–1.10; NS)
Insomnia	0.94 (0.87–1.02; NS)	0.92 (0.76–1.12; NS)	1.001 (0.83–1.21; NS)
CAD	0.98 (0.90–1.06; NS)	0.99 (0.82–1.20; NS)	0.99 (0.81–1.21; NS)
BMI	1.05 (0.92–1.21; NS)	1.02 (0.73–1.42; NS)	1.04 (0.74–1.47; NS)
Type II diabetes	1.07 (0.96–1.19; NS)	1.00 (0.77–1.30; NS)	1.13 (0.86–1.48; NS)
Height (control variable)	1.29 (0.88–1.88; NS)	1.02 (0.40–2.58; NS)	1.15 (0.46–2.88; NS)

Note: Tests were done including only suicides of ≥90% European ancestry. Citations for discovery GWAS for PRS calculations are presented in Table S2. In the logistic regressions, covariate effects are included for sex, age at death, and 10 ancestry principal components. The outcomes modeled are as follows: HFR status in the HFR versus UFR model; LFR status in the LFR versus UFR model; HFR status in the HFR versus LFR model. All results with at least nominally significant p values are in bold type.

[a]Indicates significance at a false discovery rate (FDR) of <0.05 across all pairwise tests.

[b]Indicates significance at a false discovery rate (FDR) of <0.10 across all pairwise tests.

shown). We observed increases in prevalence of all psychiatric diagnostic domains among the suicides with presence of accidental trauma/PTSD. These cases also showed increased prevalence in diagnoses related to pain, sleep disorders, obesity, and cardiovascular disease. Similar increases across psychiatric and medical diagnostic domains were observed when stratifying by suicide attempts, and when stratifying by presence of depression diagnoses.

Polygenic risk post hoc results when stratifying by young age at death showed associations with PRS of suicide death, but attenuated when compared to our primary finding with the HFR group (Table 4). Results using general linear models and testing quantitative age at death showed this same pattern of significant effects (data not shown). Stratifying on presence of accidental trauma/PTSD resulted in only a nominal association with polygenic risk of suicide death, in addition to associations with anxiety and ADHD. Stratifying on suicide attempts resulted in nominal elevations of polygenic risk for suicide attempt and risk taking, but even less evidence for association with polygenic risk for suicide death. None of the post hoc results duplicated the HFR association with PRS for PTSD. When stratifying on depression diagnoses, results were similar to those seen for stratification on prior suicide attempts, but not the strong suicide death or PTSD associations seen with the HFR group.

4 | DISCUSSION

Recent progress has been made in understanding genetic risks that may contribute to suicidal behavior and suicide death (Campos et al., 2020; Coon et al., 2020; Docherty et al., 2020, 2021; Erlangsen et al., 2018; Kious et al., 2021; Levey et al., 2019; Mullins et al., 2019; Otsuka et al., 2019; Ruderfer et al., 2019; Sokolowski, Wasserman, & Wasserman, 2014; Strawbridge et al., 2019), although major knowledge gaps remain. In particular, suicide is clearly heterogeneous, with likely variation in the degree of genetic risk among individuals. What characteristics might associate with stronger genetic risk of suicide death? Prior work studying suicide attempt might suggest diagnoses related to depression (Mullins et al., 2019), but this hypothesis is less clear for suicide death, which has shown genetic risk associations with other psychiatric diagnoses (Docherty et al., 2020). Identifying and characterizing a subgroup of suicide deaths with increased genetic risk could accelerate gene discovery efforts and serve as a starting point for additional identification of specific risk subgroups.

In this study, we used the deep genealogical data in the Utah Population Database (UPDB) to identify and characterize a subgroup of suicide deaths with HFR. The genealogical data allowed for ascertainment of unique high-risk extended families distinct from the close family relationships traditionally studied in other data resources where shared family environment and genetics both contribute to risk (Brent, Bridge, Johnson, & Connolly, 1996; Brent & Mann, 2005; Kendler, Ohlsson, Sundquist, Sundquist, & Edwards, 2020). High-risk status of extended families is instead unlikely to have a significant contribution from shared family environment and is primarily driven by familial genetic risk. Suicides linked to these high-risk families therefore represent a potential subgroup with increased genetic risk. Our analyses indicated that suicide is strongly familial. Over 90% of Utah suicide deaths linked to the ~2% of extended families at

TABLE 4 Post hoc polygenic risk tests of suicide deaths selecting on measured variables independent of familial status

Odds ratio (95% CI, *p*-value)				
Polygenic risk score	Young age at death[a] (*n* = 1,571 vs. 1,579)	Accidental trauma + PTSD (*n* = 2042 vs. 1,108)	Suicide attempts (*n* = 636 vs. 2,514)	Depression diagnoses (*n* = 1,567 vs. 1,583)
Suicide death	**1.26 (1.07–1.48, .006)**[b]	**1.19 (1.01–1.42, .04)**	1.18 (0.96–1.45, NS)	1.17 (0.99–1.38, NS)
Suicide attempt	1.02 (0.93–1.11, NS)	1.05 (0.95–1.15, NS)	**1.13 (1.01–1.26, .04)**	1.12 (1.03–1.23, .01)
MDD	1.03 (0.94–1.13, NS)	1.03 (0.82–1.29, NS)	1.03 (0.92–1.15, NS)	1.08 (0.99–1.14, NS)
Anxiety	0.95 (0.88–1.01, NS)	**1.14 (1.06–1.22, .0006)**[c]	**1.10 (1.01–1.20, .04)**	1.07 (0.99–1.14, NS)
PTSD	1.05 (0.93–1.18, NS)	1.07 (0.94–1.22, NS)	1.02 (0.87–1.19, NS)	1.10 (0.97–1.25, NS)
ADHD	1.06 (0.99–1.14, NS)	**1.15 (1.07–1.23, .0002)**[c]	1.05 (0.96–1.15, NS)	1.08 (1.10–1.16, .03)
Bipolar	0.94 (0.77–1.15, NS)	0.88 (0.72–1.08, NS)	1.25 (0.96–1.63, NS)	1.27 (1.03–1.54, .03)
Schizophrenia	1.17 (1.01–1.36, .04)	0.85 (0.73–1.00, NS)	1.21 (0.99–1.47, NS)	1.10 (0.94–1.29, NS)
Risk taking	1.06 (0.98–1.14, NS)	1.02 (0.94–1.11, NS)	**1.11 (1.01–1.22, .04)**	1.04 (0.96–1.13, NS)
Drinks per week	0.99 (0.92–1.07, NS)	1.02 (0.95–1.11, NS)	1.00 (0.91–1.10, NS)	0.97 (0.89–1.04, NS)
Insomnia	1.02 (0.94–1.10, NS)	1.03 (0.95–1.12, NS)	1.04 (0.95–1.15, NS)	1.04 (0.97–1.13, NS)
CAD	**1.09 (1.01–1.18, .03)**	1.08 (0.99–1.17, NS)	0.96 (0.87–1.06, NS)	0.96 (0.89–1.04, NS)
BMI	0.99 (0.87–1.13, NS)	1.02 (0.89–1.17, NS)	0.91 (0.77–1.08, NS)	0.94 (0.82–1.08, NS)
Type II diabetes	0.97 (0.88–1.01, NS)	**1.15 (1.03–1.28, .02)**	1.02 (0.89–1.16, NS)	1.01 (0.90–1.12, NS)
Height (control variable)	0.83 (0.68–1.08, NS)	0.91 (0.63–1.33, NS)	0.92 (0.58–1.42, NS)	1.09 (0.76–1.58, NS)

Note: Young age at death, presence of accidental trauma and/or PTSD diagnoses, and presence of documented suicide attempts were associated with HFR suicides. Presence of depression diagnoses, not associated with HFR diagnoses, was included as a comparison because of its importance in prior published literature. Tests used only suicides with >90% European ancestry. In the logistic regressions, covariate effects of sex and 10 additional ancestry principal components were included. Age of death was additionally used as a covariate for analyses of these variables: presence of accidental trauma + PTSD, suicide attempt, and depression diagnoses. All results with at least nominally significant *p* values are in bold type.

[a]Younger than mean age of 41.22 years.

[b]Indicates significance at a false discovery rate (FDR) of <0.10 across all pairwise tests.

[c]Indicates significance at a false discovery rate (FDR) of <0.05 across all pairwise tests.

significantly elevated risk for suicide death, results that are consistent with broader population-wide findings in Utah data (Bakian et al., 2021). The characteristics of these HFR suicide deaths were the focus of this study, compared to those linked to the genealogies but not linked to any high-risk families (low-familial-risk or LFR suicides) and those with UFR (UFR suicides).

Demographic results indicated that suicide deaths that link to the genealogical records, independent of high-risk vs. low-risk status, are more likely to be of European descent. This result is not surprising given that the genealogical records are from historical records of European descent individuals who settled in the area in the mid-1800s (https://uofuhealth.utah.edu/huntsman/utah-population-database/). UFR suicides were, by contrast, less European (88.24%), although this percentage still reflected the predominantly European race distribution in the Utah population. This group may represent more recent in-migration to Utah.

Demographic results also revealed an association between HFR suicides and significantly lower age at death (39.34 years). Of interest, LFR suicides had a significantly higher average age at death (49.10 years), almost 10 years older at death on average than HFR suicides. The age results support possible increased genetic etiology in the HFR group and increased environmental etiology in the LFR group, as individuals who die at a younger age do not have as much opportunity to experience influences of specific environmental life stressors, or the same accumulated burden of stressors over time. The result that LFR suicides are significantly older at death is additionally an important check for bias in our study. Extended family structures in our genealogical data (regardless of high-risk or low-risk status) are sparser in the top generations, and include more individuals in the bottom, younger generations. Therefore, younger age at death could have been systematically associated simply with linkage to genealogical data, as follows. The greater number of individuals in bottom generations in more recent birth cohorts would be associated with the opportunity to observe more suicides, and for these more recent birth cohorts, death at older ages would be impossible. However, the finding of significantly older age at death among LFR suicides, which are also linked to the genealogy data, suggests the association in the HFR group of young age at death is not simply a reflection of this familial data structure issue.

We chose domains of clinical diagnoses based on published associations with suicidal behavior. Clinical associations included prior suicide attempts, depression, anxiety, ADHD, substance abuse, bipolar disorder, and psychosis (Dome, Rihmer, & Gonda, 2019; Girgis, 2020; Ilgen et al., 2009; Østergaard, Nordentoft, & Hjorthøj, 2017; Thompson et al., 2020; Yeh et al., 2019). Trauma exposure and PTSD have also been previously implicated (Björkenstam, Kosidou, &

Björkenstam, 2017; Johansson, Stenlund, Bylund, & Eriksson, 2012; Leardmann et al., 2013); in our data, this domain was analyzed as presence of accidental trauma and PTSD diagnoses together, as PTSD diagnoses in this population-ascertained sample were too uncommon for separate analysis. Diagnoses associated with pain and sleep disorders were included as medical diagnoses also associated with psychopathology, and with evidence for suicide risk (Chu, Nota, Silverman, Beard, & Bjorgvinsson, 2019; Sommer, Blaney, & El-Gabalawy, 2019). We additionally studied common chronic medical conditions with published suicide associations, including of cancer (Voskarides & Chatzittofis, 2019), cardiovascular disease (Thordardottir et al., 2020; Zhong et al., 2020), and obesity (Knowles et al., 2018). For tests of polygenic risks, we chose summary statistics from large genetic studies (at least 10,000 participants) of disorders and traits related to these diagnostic categories.

In our clinical data, HFR suicide deaths when compared to UFR and LFR suicides were associated with modest increases in the frequency of documented prior suicide attempts and with increased accidental trauma and PTSD diagnoses, but with no other psychiatric or medical condition. This group also showed a strikingly high association with PRS for suicide death, and lesser associations with PRS of PTSD, suicide attempt, and risk taking. These HFR results suggest that there is a potential subset of younger individuals genetically vulnerable to suicide, and that additional study of the importance of exposure to trauma and response to trauma is warranted.

In addition to the HFR suicides, we had the opportunity to study suicide deaths with sufficient genealogical data but no connection to extended high-risk families. While these suicides make up a surprisingly small number of cases ($N = 147$), they are an important subgroup. In comparison to HFR and UFR suicides, this group was substantially older at death on average. The LFR suicides were interestingly associated with fewer clinical diagnoses of depression, anxiety, sleep, pain, and cardiovascular disease. These associations were present even though the models were adjusted for significant age effects. The polygenic risk results supported the clinical findings for depression, where PRS was markedly lower in the LFR group. The patterns of clinical and genetic associations with the LFR group support the conclusion that this is a subset potentially without elevation in the specific genetic risk of suicide, and less genetic risk of depression. As it grows in size with our ongoing collection of samples and linking of data, this group may be useful for future more detailed studies of environmental factors leading to suicide risks.

The deep Utah genealogical data allow us to study familial risk to an unprecedented degree, and to explore correlates of elevated genetic risk of suicide death. However, extended familial risk is most often unknown, and is usually unavailable even in other research resources. In addition, PRS for suicide death as an identifier of genetic risk is, at least at this point in time, useful only as a tool to study group effects, and not as an individual predictor of risk (Docherty et al., 2021; Kious et al., 2021). We therefore conducted post hoc tests of easily obtained measured characteristics that were significantly associated with HFR suicides in our study to understand if any could serve as reasonable proxies for defining a group at elevated genetic risk. An analysis of young age at death independent of HFR status showed a significant, but attenuated association with polygenic risk of suicide death. The association with polygenic risk of suicide death was even less apparent when stratifying only on presence of accidental trauma/PTSD. Stratification on presence of prior suicide attempts did not reproduce the association with polygenic risk of suicide death, suggesting that prior attempt may be less important than trauma when considering potential elevated genetic risk. Because of strong associations in the published literature, we included an additional post hoc test stratifying on presence of depression diagnoses. Results for this stratification most closely matched stratification on prior suicide attempt, and did not reveal the strong results with PRS for suicide death, or the association with PRS for PTSD found in the HFR suicides.

4.1 | Limitations

The direct comparison of HFR to LFR suicides was hampered by lower statistical power due to the small size of the LFR group, although the strongest measured phenotype and polygenic associations were still present. This study pursues the unexplored territory of describing a subset of suicides hypothesized to be at higher genetic risk through their linkage to unique, genetically driven, extended high-risk families. Because of the exploratory nature of this work, we have retained findings of nominal significance, additionally denoting significance at false discovery rates of 0.05 and 0.10. Polygenic risk associations of higher suicide death in HFR suicides and of lower depression in LFR suicides were sufficiently strong to reach significance. We acknowledge that interpretation of other nominally significant results will require reanalysis with larger sample sizes in the future.

Finally, we note that we randomly omitted one in each pair of closely related cases (pi-hat ≥0.125), a threshold commonly used for controlling for cryptic relatedness in genetic studies. However, there remain many distantly related suicide deaths in our sample; the cases are therefore not strictly independent. Could genome-wide sharing of SNP data among these distantly related individuals lead to spurious significant findings? Our results suggest this is highly unlikely; if this bias had been present, we should have observed across-the-board sharing from all traits under genetic control in our HFR and LFR groups due simply to relatedness. Instead, we see quite distinct patterns of results.

5 | CONCLUSIONS

Better understanding of individuals at high risk for suicide death is of utmost importance. Our results confirmed that extended familial risk of suicide death can uniquely define a subset of suicide deaths at greater genetic risk. Our results also revealed remarkable familiality of suicide death. The HFR group was significantly younger at death. Polygenic associations confirmed the hypothesized increase in polygenic risk specific to suicide death, and furthermore showed this risk

is relatively specific to suicide and not strongly associated with genetic risk of other psychopathology. Modest increases were also observed for PRS of PTSD, and to a lesser extent, PRS for suicide attempt and risk taking, potentially providing guidance for future studies of clinical risk correlates associated with elevated genetic risk of suicide.

Suicides with a lack of extended familial risk were ~10 years older on average at death, had fewer diagnoses associated with depression and anxiety, and had significantly lower polygenic risk of depression. This subgroup has potential for future studies of non-genetic risk factors leading to suicide death. Finally, in the absence of available information on extended familial risk, and acknowledging PRS for suicide death should not be used for individual prediction, further study of youth with trauma exposures and PTSD as having possible increase in genetic liability for suicide death may be warranted.

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CONFLICT OF INTEREST

Co-author Dr Qingqin Li is employed by Janssen Research & Development, LLC. All other authors have no financial relationships with commercial interests.

DATA AVAILABILITY STATEMENT

Due to their potentially identifying nature, specific pedigree structures are not available. However, pairwise kinship data among suicide deaths can be obtained by contacting the authors. Statistics to enable polygenic risk scoring from the Utah GWAS of suicide death (Docherty et al., 2020) can also be obtained by contacting the authors. Polygenic risk scores of psychiatric and medical traits used in this study can be downloaded from LD Hub (http://ldsc.broadinstitute.org/ldhub/).

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