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Supplementary information

Exome sequencing of individuals with Huntington's disease implicates FAN1 nuclease activity in slowing CAG expansion and disease onset

In the format provided by the authors and unedited

Supplementary information

McAllister et al.

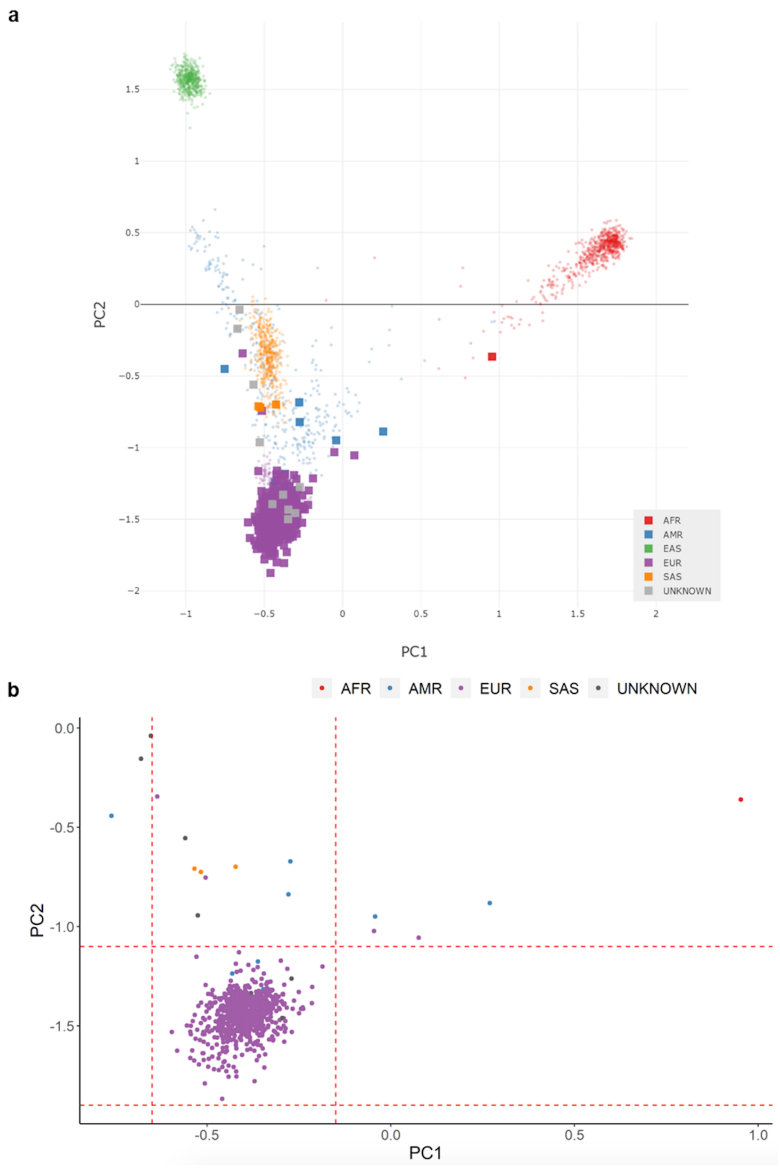
Supplementary Figures 1-4

Supplementary Tables 1-10

Supplementary References

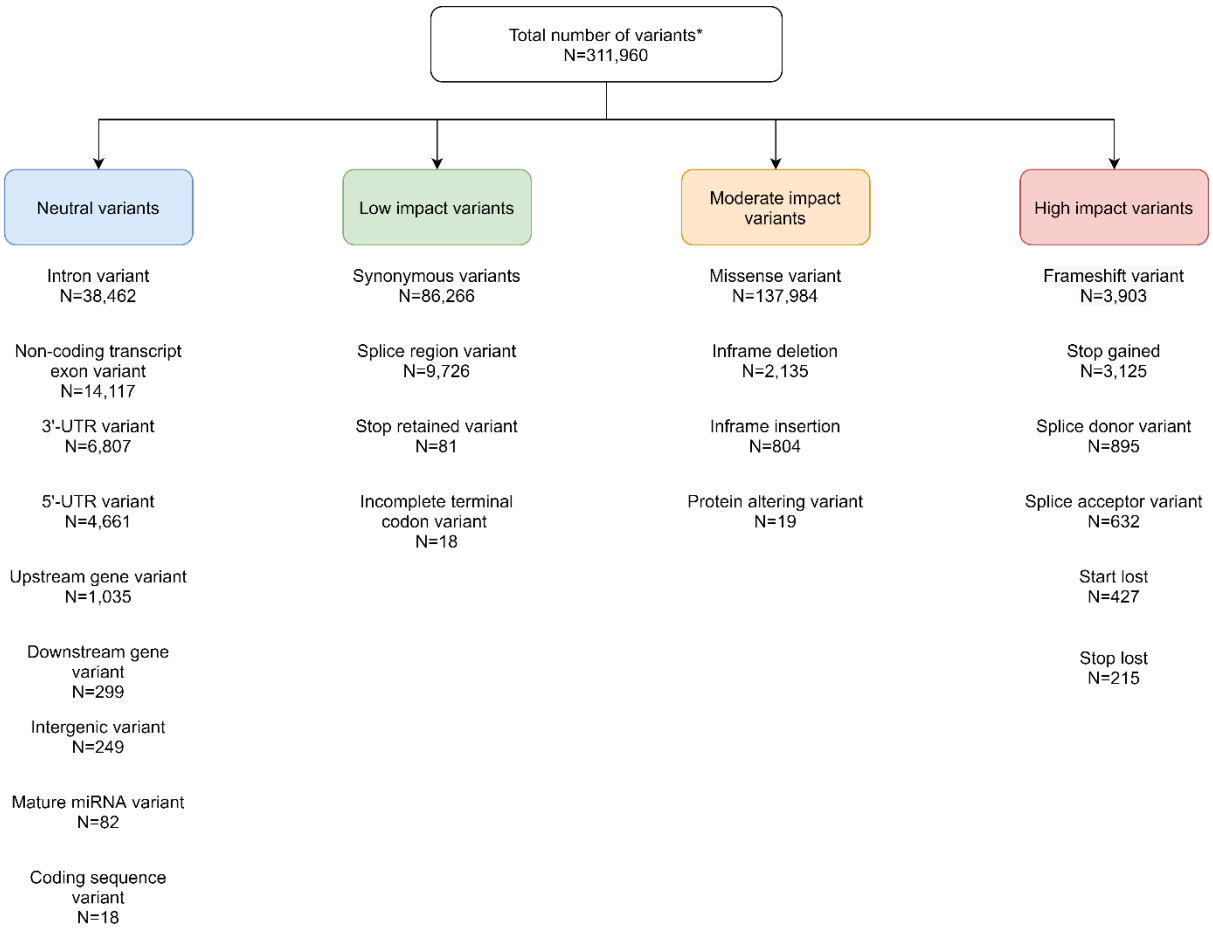
Supplementary source data

Members of Consortia



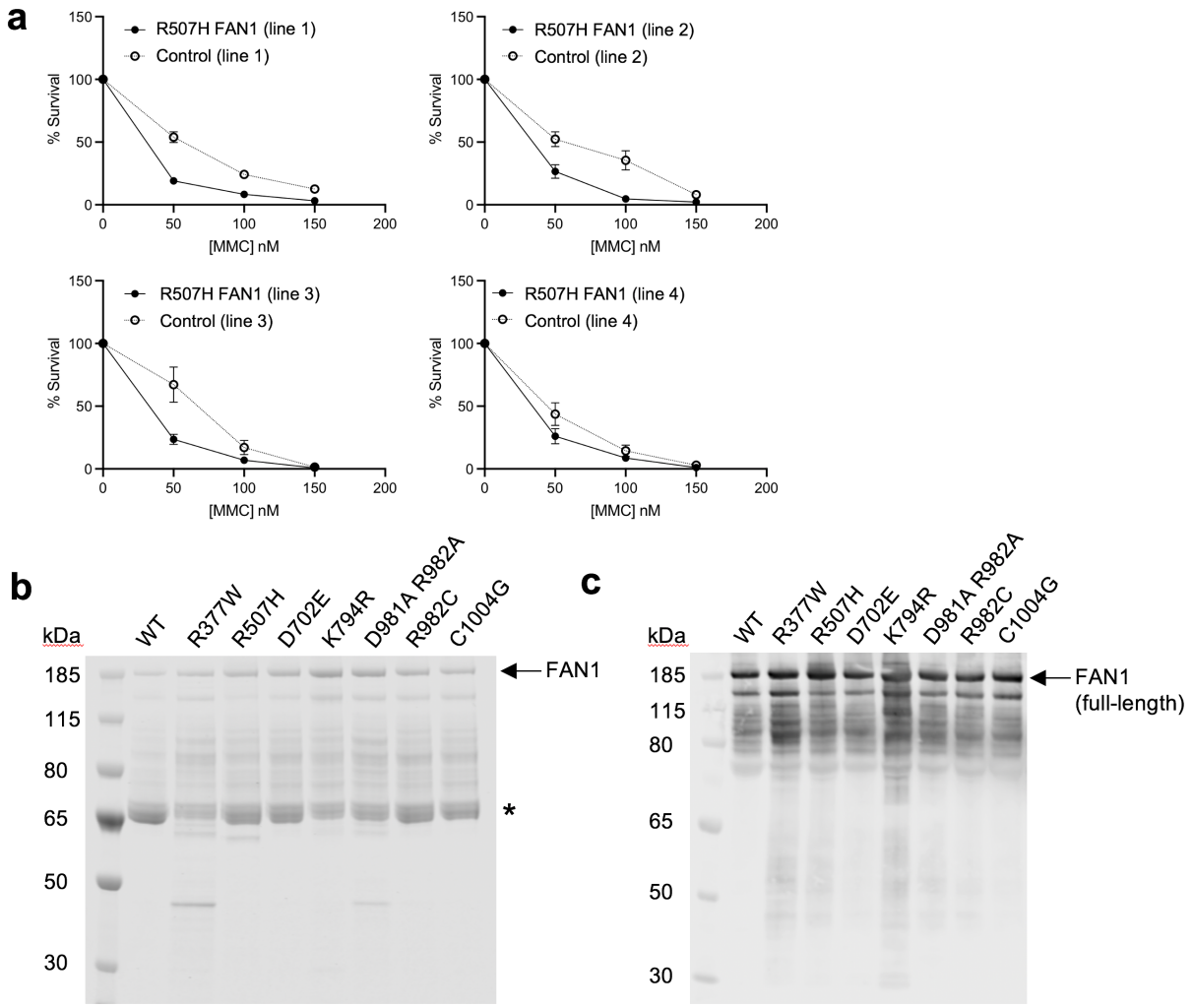
Supplementary Fig. 1: Individuals of European Ancestry were selected for downstream analysis

a, Principal component analysis and estimated ancestries based on the 1,000 genome project as calculated by Peddy[1] for N=725 individuals passing initial quality control (See Fig. S1a). Individuals of European ancestry in purple.
b, Magnified area of the principal component analysis (PC1 and PC2) from (a). Individuals with predicted European ancestry enclosed within the rectangle bordered by dotted lines were retained in analyses (N=700).
Key: AFR, African; AMR, Ad Mixed American; EAS, East Asian; EUR, European; SAS, South Asian



Supplementary Fig. 2: The types and predicted functional impacts of all variants identified through exome sequencing

All variants compared with the hg19 human genome were annotated using the pipeline in Fig. S1b and divided into four classes based on predicted functional impact. For variants with multiple annotations, the most damaging annotation (listed first in variant effect predictor (VEP)) was used. Total variant numbers are shown for the 683 exomes which passed quality control.

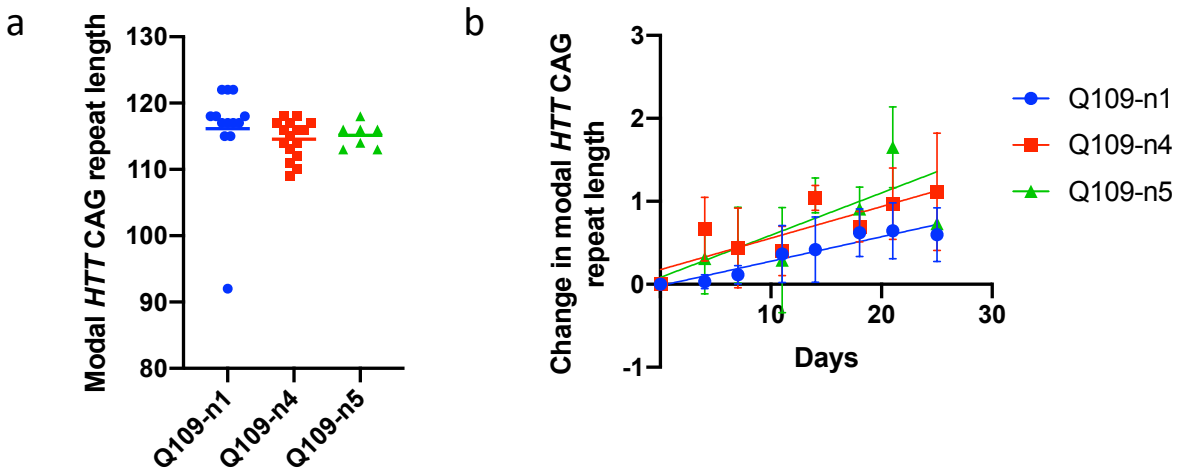


Supplementary Fig. 3: HD lymphoblastoid cells carrying R507H are sensitive to mitomycin C. Partial purification of wild-type and FAN1 variants.

a, 4 lymphoblastoid cell lines derived from individuals with HD carrying a heterozygous R507H FAN1 variant were grown alongside control HD lines with homozygous wild-type FAN1 matched for age and pure CAG length and treated with a single dose of 0-150 nM mitomycin C. Survival (% of untreated live cell count) at 7 days shown for each line (mean, s.e.m., N=3 independent experiments).

b, NusA-His-tagged full-length FAN1 proteins (wild-type (WT) and variants as shown) were expressed in *E. coli* and partially purified using cobalt-agarose. Samples were run on 4-12% Bis-Tris SDS-PAGE and stained with Coomassie blue. Expected size of NusA-His-FAN1 is 175.9 kDa as indicated. FAN1 band intensities were used to normalise the amounts of FAN1 used in nuclease assays. Main contaminants (*) identified by mass spectrometry as *E. coli* chaperones ArnA and DnaK. Further purification of FAN1 proteins was attempted but active protein yields were low.

c, Immunoblot of WT and FAN1 variants run on 4-12% Bis-Tris SDS-PAGE as in **(b)**. Primary antibody was sheep polyclonal to FAN1 (CHDI). Full-length FAN1 is seen along with multiple degradation products.



Supplementary Fig. 4: Q109 HD iPSC lines have unstable *HTT* CAG repeats that expand over time in culture

a, Modal CAG repeat lengths for the expanded *HTT* allele of multiple independent, low passage, sub-clones of three independent clonal lines of CS09iHD109 (Q109) HD iPSCs (Q109-n1, n=13; Q109-n4, n=16; Q109-n5, n=7). CAG repeat length mosaicism is demonstrated. Horizontal lines represent means.

b, Modal *HTT* CAG repeat lengths against time in culture as iPSCs for three independent clonal lines of CS09iHD109 (Q109) cells (n1, n4 and n5). Combined data are shown for multiple independent sub-clones of each clonal line (Q109-n1, N=4; Q109-n4, N=3; Q109-n5, N=3). Mean ± s.e.m. shown.

Supplementary Tables

Study Group	N	Sex (% male)[a]	CAG length	Age at Motor Onset (AMO)[b]	Residual AMO[b]
REGISTRY-HD	465	46.6%	42.9 (2.2)	48.4 (16.4)	-0.8 (13.4)
Early (REGISTRY-HD)	214	45.3%	43.4 (2.3)	33.7 (7.8)	-13.9 (4.9)
Late (REGISTRY-HD)	207	48.3%	42.3 (1.8)	63.9 (7.7)	+12.7 (4.2)
PREDICT-HD	218	38.1%	43.3 (2.8)	47.1 (9.8)	-1.0 (5.9)
More severe (PREDICT-HD)	101	31.7%	43.2 (2.7)	46.1 (9.5)	-1.7 (5.5)
Less severe (PREDICT-HD)	115	42.6%	43.4 (3.0)	53.6 (10.1)	+5.0 (5.9)

(a) One individual in the late REGISTRY-HD group was of unknown sex and not included in the sex column
(b) AMO and residual AMO were calculable for all in the REGISTRY-HD group. For the PREDICT-HD group, AMO and AMO residual were calculable for 93 individuals passing initial QC for dichotomous analyses, before phenotype selection (80 were in the more severe group; 11 in the less severe group; 2 in neither extreme group)

Supplementary Table 1: Demographic details for individuals passing quality control and included in the exome sequencing analyses.

Total N=683 (465 REGISTRY-HD group; 218 PREDICT-HD group). Not all individuals were part of the extreme phenotype groups (early/late in REGISTRY-HD, more severe/less severe in PREDICT-HD) after correction for pure CAG repeat lengths following sequencing. Mean (standard deviation) shown for pure CAG length after sequencing, age at motor onset (AMO) and residual AMO.

CAG tract sequence (expanded *HTT*)	Predicted early or worse TMS/SDMT (more severe)	Predicted late or better TMS/SDMT (less severe)
Canonical (CAACAG)	98	111
$(CAACAG)_2$	1	2
$CAC(CAG)_3CAACAG$	0	2
No interruption (pure CAG)	2	0

Supplementary Table 2: CAG repeat tract sequences for PREDICT-HD group, derived from exome sequencing data

Whole-exome sequencing data were extracted and manually assessed to determine the 3' sequence of the CAG repeat tract in pathogenic *HTT* alleles. It was not possible to determine full allelic structures as read lengths were 75 bp. Phase could be determined for atypical alleles as wild-type CAG length was short enough to be effectively captured. The presence or absence of interrupting CAA triplets was used as a covariate in exome analyses. N=216 (those from the dichotomous group).

a

Gene	Dichotomous group (N=637)			Continuous group (N=558)		
	NS	NSD20	LoF	NS	NSD20	LoF
FAN1	**2.32E-04**	*6.61E-04*	2.17E-01	*1.09E-03*	*9.06E-04*	3.40E-01
FAN1 (no R377W/R507H)	*3.76E-02*	*4.37E-02*	2.17E-01	2.85E-01	3.02E-01	3.40E-01

b

Modifier	Top SNP	Location (hg19)	FAN1 protein	p value, all NSD20 variants	p value, all NSD20 variants excluding R377W & R507H
AM1	rs150393409	15:31202961:G:A	R507H	**7.74E-19**	3.89E-01
AM2	rs8034856	15:31240957:T:C	-	7.04E-01	5.67E-01
AM3	rs151322829	15:31197995:C:T	R377W	**2.31E-06**	6.68E-01
AM5	rs118089305	15:31204637:C:T	-	7.96E-02	3.09E-01

Supplementary Table 3: Exome sequencing detects rare variation in *FAN1* associated with altered HD onset that was previously uncaptured by GWAS.

a, *FAN1* retains nominal significance in Optimal Sequence Kernel Association Tests (SKAT-O) of rare coding variants (minor allele frequency < 1%) and HD phenotypes after the exclusion of the R377W and R507H variants previously identified by GeM-HD GWAS (row 2). Variant numbers were regressed on either dichotomous early/more severe or late/less severe phenotypes (N=637; logistic regression) or a continuous phenotype of residual age at motor onset (N=558; linear regression). Phenotypes were corrected for non-canonical *HTT* CAG repeats in expanded alleles by using either a covariate in logistic analyses, or pure CAG lengths from sequencing in continuous analyses. Three different variant groups were tested: all non-synonymous (NS), non-synonymous and predicted damaging to protein function (NSD20; CADD PHRED score ≥ 20), and loss-of-function (LoF). Significant associations in bold ($p < 6.4E-4$, Bonferroni correction for 13 genes and 6 tests; see also Table 1); nominally significant associations in italics ($p < 0.05$)

b, The burden of rare damaging variation in FAN1 is not significantly associated with any of the lead variants from GeM-HD GWAS, after removal of R377W and R507H. Binomial generalised linear models were constructed running the presence of a non-synonymous damaging (NSD20) variant (0 or 1) detected through exome sequencing on the number of copies of each *FAN1* modifier SNP detected through GWAS (0, 1 or 2). These were compared to models running the intercept only, and an ANOVA test was used to compare the two models, for which the *p* values are shown above. AM1, AM2, AM3 and AM5 refer to the independent *FAN1* modifiers previously reported. Note for AM5, the second tagging SNP was used as opposed to rs79213781 as imputation for this SNP was not available in our GWA data. N=441: all those in our dataset with exome sequencing and GWAS data.

		Dichotomous group (N=637)			Continuous group (N=558)		
Chr	Gene	NS	NSD20	LoF	NS	NSD20	LoF
2A	*ANKAR*	8.47E-01	8.28E-01	NA	8.44E-01	6.91E-01	7.86E-01
2A	*ASNSD1*	9.01E-01	8.20E-01	NA	5.61E-01	6.97E-01	NA
2A	*ORMDL1*	3.77E-01	4.34E-01	NA	4.81E-01	5.29E-01	NA
2A	*OSGEPL1*	8.16E-01	8.28E-01	7.80E-01	7.79E-01	7.81E-01	8.47E-01
2A	*PMS1*	**2.72E-02**	**2.65E-03**	3.13E-01	2.62E-01	1.08E-01	NA
3A	*EPM2AIP1*	4.87E-01	4.51E-01	NA	1.00E+00	1.00E+00	NA
3A	*GOLGA4*	8.36E-01	6.72E-01	**3.40E-03**	6.59E-01	2.18E-01	6.30E-02
3A	*LRRFIP2*	3.57E-01	4.91E-01	NA	3.62E-01	8.85E-01	NA
3A	*MLH1*	1.72E-01	5.58E-02	NA	4.99E-01	7.45E-01	NA
3A	*TRANK1*	4.10E-01	5.42E-01	8.98E-01	1.97E-01	3.63E-01	6.07E-01
3A	*C3orf35*	3.21E-01	2.17E-01	2.16E-01	2.01E-01	1.63E-01	1.35E-01
3A	*ITGA9*	1.00E+00	8.51E-01	NA	8.76E-01	8.99E-01	NA
5A	*ANKRD34B*	1.80E-01	8.61E-01	NA	1.64E-01	6.76E-01	NA
5A	*DHFR*	1.05E-01	9.83E-02	NA	1.54E-01	1.42E-01	NA
5A	*FAM151B*	1.51E-01	1.45E-01	NA	5.79E-01	5.77E-01	NA
5A	*MSH3*	5.96E-02	2.78E-01	**9.51E-03**	3.00E-01	6.35E-01	1.09E-01
5A	*MTRNR2L2*	2.22E-01	NA	NA	8.12E-01	NA	NA
5B	*GPR151*	5.48E-01	4.20E-01	5.12E-01	2.65E-01	2.54E-01	2.12E-01
5B	*PPP2R2B*	1.61E-01	2.52E-01	NA	4.82E-01	7.36E-01	8.41E-01
5B	*TCERG1*	**1.25E-02**	4.54E-01	NA	**2.74E-03**	2.76E-01	NA
7A	*AIMP2*	5.16E-02	1.75E-01	7.17E-01	1.66E-01	2.08E-01	1.58E-01
7A	*ANKRD61*	5.25E-01	1.00E+00	2.47E-01	5.05E-01	7.08E-01	6.44E-01
7A	*CCZ1*	1.55E-01	1.84E-01	NA	2.80E-01	2.88E-01	NA
7A	*CYTH3*	8.43E-02	7.99E-02	NA	1.01E-01	1.19E-01	NA
7A	*EIF2AK1*	6.63E-01	7.28E-01	NA	7.05E-01	7.31E-01	NA
7A	*OCM*	8.61E-01	8.65E-01	1.00E+00	1.00E+00	1.00E+00	8.54E-01
7A	*PMS2*	1.00E+00	9.00E-01	5.55E-01	5.59E-01	3.51E-01	1.33E-01
7A	*RSPH10B*	NA	NA	NA	NA	NA	NA
7A	*RSPH10B2*	NA	NA	NA	8.92E-01	NA	NA
7A	*USP42*	7.18E-01	2.49E-01	NA	1.00E+00	3.89E-01	NA
8A	*RRM2B*	1.69E-01	NA	NA	**2.26E-02**	NA	NA
8A	*UBR5*	7.47E-01	7.23E-01	NA	4.11E-01	3.88E-01	NA
11A	*CCDC82*	5.27E-01	NA	NA	6.09E-01	9.01E-01	NA
11A	*JRKL*	2.48E-01	2.42E-01	NA	7.74E-02	7.07E-02	NA
11A	*MAML2*	1.00E+00	8.94E-01	2.08E-01	5.16E-01	4.62E-01	1.31E-01
11B	*SYT9*	1.05E-01	1.13E-01	NA	4.20E-01	4.12E-01	NA
12A	*CORO1C*	8.75E-01	8.69E-01	8.33E-01	6.78E-01	6.66E-01	8.44E-01
12A	*FICD*	3.41E-01	3.42E-01	NA	5.86E-01	7.55E-01	NA
12A	*ISCU*	NA	NA	NA	NA	NA	NA
12A	*SART3*	9.02E-01	7.23E-01	NA	8.15E-01	4.32E-01	NA
12A	*SELPLG*	5.31E-01	8.55E-01	NA	7.91E-01	6.61E-01	NA
12A	*SSH1*	6.77E-02	1.45E-01	5.09E-01	2.77E-01	4.13E-01	9.81E-01
12A	*TMEM119*	5.56E-01	NA	NA	5.28E-01	NA	NA
15A	*FAN1*	**2.32E-04**	**6.61E-04**	2.17E-01	**1.09E-03**	**9.06E-04**	3.40E-01
15A	*MTMR10*	8.11E-01	7.95E-01	NA	3.01E-01	2.77E-01	NA
15A	*TRPM1*	**9.11E-03**	**3.24E-03**	2.28E-01	**1.41E-02**	**6.90E-03**	3.09E-01
16A	*GSG1L*	9.05E-01	9.13E-01	NA	4.09E-01	4.35E-01	NA
18A	*ALPK2*	6.47E-01	1.86E-01	4.06E-01	4.74E-01	8.83E-01	8.50E-01
18A	*MIR122*	NA	NA	NA	NA	NA	NA
19A	*C19orf68*	5.15E-02	5.41E-02	NA	1.80E-01	1.66E-01	NA
19A	*LIG1*	9.47E-02	7.07E-02	5.09E-01	**3.63E-02**	**2.30E-02**	5.16E-01
19A	*PLA2G4C*	8.02E-01	8.68E-01	NA	3.99E-01	7.39E-01	NA

Supplementary Table 4: Candidate gene analysis of rare coding variant associations with HD phenotype for all genes found at candidate modifier loci in GeM-HD GWAS.

Optimal Sequence Kernel Association Tests (SKAT-O) of rare coding variants (minor allele frequency < 1%) and HD phenotypes. Gene-wide variant numbers were regressed on either dichotomous early/more severe or late/less severe phenotypes (N=637; logistic regression) or a continuous phenotype of residual age at motor onset (N=558; linear regression). Phenotypes were corrected for non-canonical *HTT* CAG repeats in expanded alleles by using either a covariate in logistic analyses, or pure CAG lengths from sequencing in continuous analyses. Three different variant groups were tested: all non-synonymous (NS), non-synonymous and predicted damaging to protein function (NSD; CADD PHRED score ≥ 20), and loss-of-function (LoF). Chromosomal loci from GeM-HD GWAS are indicated. Nominally significant associations in bold ($p < 0.05$). Note that several genes from GeM-HD GWAS loci were not annotated in exome sequencing data and hence not included: *OSGEPL1-AS1* (2A); *JRKL-AS1* + *MIR1260B* (11A); *LOC102723562* (12A); *HERC2P10* + *LOC100288637* + *MIR211* (15A) + *MIR3591* (18A). See also Table 2.

	Early/more severe			Late/less severe		
Gene	NS	NSD20	LoF	NS	NSD20	LoF
PMS1	4	2	0	15	14	1
MLH1	11	10	0	11	5	0
MSH3	8	8	0	19	14	7
DHFR	0	0	0	3	3	0
TCERG1	45	6	0	68	3	0
PMS2	14	2	1	14	1	0
RRM2B	1	0	0	5	0	0
UBR5	7	7	0	5	5	0
CCDC82	4	0	0	4	0	0
SYT9	8	8	0	3	3	0
FAN1	47	34	1	18	11	0
GSG1L	2	2	0	2	2	0
LIG1	11	10	1	16	13	0

Supplementary Table 5: Burden of rare non-synonymous variants of different types in candidate HD modifier genes in the early/more severe and late/less severe phenotype groups

The gene-wide total counts of rare (minor allele frequency <1%) non-synonymous (NS), non-synonymous and predicted damaging to protein function (NSD20; CADD PHRED score ≥ 20) or predicted loss-of-function (LoF) variants in candidate modifier genes from GeM-GWAS are shown for the early/more severe (N=315) and late/less severe (N=322) phenotype groups of the dichotomous association analysis (total N=637). Early/more severe corresponds to early or predicted early onset or high TMS or SDMT. Late/less severe corresponds to late or predicted late onset or low TMS or SDMT. CADD score predicts how damaging individual variants are to protein function. CADD score ≥ 20 implies a variant is in the top 1% predicted most damaging substitutions in the human genome (dbSNFP v4.0[2,3]). See also Table 1.

a

Coordinates	Variant	MAF	CADD score	Early/more severe	Late/less severe
2:190660537:G:A	E59K	4.67E-03	20.4	2	3
2:190660586:C:T	T75I	1.05E-03	24.0	0	4
2:190670391:C:G	T110R	6.17E-05	24.0	0	1
2:190670396:A:G	T112A	8.81E-06	25.6	0	1
2:190717470:CA:C	S264*	NA	NA	0	1
2:190719296:A:G	K433R	3.54E-05	7.5	1	0
2:190719499:G:A	G501R	5.84E-04	25.8	0	1
2:190719569:T:C	L524S	0.00E+00	13.1	1	0
2:190719607:G:A	E537K	2.80E-03	22.8	0	2
2:190719704:G:A	R569Q	1.32E-04	22.1	0	1
2:190732559:T:C	Y793H	5.64E-04	14.5	0	1

b

Coordinates	Variant	MAF	CADD score	Early/more severe	Late/less severe
5:79950562:C:T	P6S	2.65E-04	18.5	0	1
5:79950677:C:G	A44G	1.96E-05	13.2	0	1
5:79952237:A:T	E82V	NA	18.0	0	1
5:79952345:A:T	N118I	4.40E-05	16.0	0	1
5:79966033:G:T	E233*	0.00E+00	48.0	0	1
5:79974830:A:G	S420G	6.16E-05	9.6	0	1
5:80021292:G:A	R454Q	5.29E-05	26.7	1	0
5:80021311:CATTT:C	IY461-462*	NA	NA	0	1
5:80040326:C:T	T552I	6.21E-05	25.4	0	1
5:80057364:G:A	NA (†)	2.64E-05	24.5	0	1
5:80063896:C:T	P681S	1.59E-03	23.6	0	1
5:80063899:G:C	V682L	3.70E-04	24.6	1	0
5:80071512:G:C	NA (†)	NA	28.3	0	1
5:80074538:G:A	NA (†)	NA	34.0	0	1
5:80074556:G:A	R779H	2.29E-04	28.7	0	1
5:80083383:G:A	NA (†)	3.52E-05	24.2	0	1
5:80088565:G:C	E853Q	6.18E-05	26.9	1	1
5:80088589:A:C	N861H	8.81E-06	24.4	0	1
5:80109433:G:T	G896*	4.40E-05	45.0	0	1
5:80109479:T:G	L911W	3.42E-03	26.4	4	2
5:80150135:T:G	D1000E	0.00E+00	22.7	1	0

(†) Predicted loss-of-function splice acceptor variants

(*) Premature stop codon loss-of-function variants

Supplementary Table 6: Rare non-synonymous coding variants in PMS1 and MSH3 identified in extreme phenotype groups of individuals with HD

Allele counts for all rare (MAF < 1%) non-synonymous coding variants in (a) PMS1 and (b) MSH3 identified through exome sequencing in the dichotomous extreme phenotype cohort (N=637). Genomic coordinates are given for hg19. Early/more severe corresponds to early or predicted early onset or high TMS or SDMT. Late/less severe corresponds to late or predicted late onset or low TMS or SDMT. CADD score predicts how damaging individual variants are to protein function. CADD score > 20 implies a variant is in the top 1% predicted most damaging substitutions in the human genome (dbSNFP v4.0[2,3]). Minor allele frequencies (MAF) taken from the European arm of gnomAD[4] v2.1.1.

Dichotomous (N=637)		Continuous (N=558)	
Gene	p	Gene	p
DMGDH	2.92E-04	*CUBN*	1.44E-04
OR4C15	4.20E-04	*ERAP2*	3.96E-04
FAN1	6.61E-04	*ZNF462*	6.18E-04
IGF1R	1.07E-03	*DENND4B*	6.60E-04
MUC6	1.55E-03	*KIAA0319*	8.79E-04
ELP2	1.87E-03	*FAN1*	9.06E-04
LAD1	2.24E-03	*FBP2*	1.06E-03
PEG3	2.34E-03	*SIPA1L2*	1.15E-03
PMS1	2.65E-03	*C9*	1.17E-03
NDOR1	2.67E-03	*NAALAD2*	1.39E-03
C2CD3	3.10E-03	*SAMD3*	1.83E-03
FBP2	3.24E-03	*MUT*	2.10E-03
TRPM1	3.24E-03	*P2RY13*	2.32E-03
RAD54L	3.35E-03	*ANXA11*	2.78E-03
ST7L	3.65E-03	*PPP2R1B*	3.22E-03

Supplementary Table 7: Exome-wide association analysis of the burden of rare, predicted damaging coding variation in genes and HD clinical phenotypes highlights *FAN1*

Exome-wide Optimal Sequence Kernel Association Tests (SKAT-O) were performed using rare (minor allele frequency < 1%), predicted damaging, non-synonymous variants (loss-of-function and/or CADD PHRED score ≥20; NSD20) collapsed on genes, and testing for association with clinical phenotypes. In the dichotomous analysis, association of phenotype (early/more severe or late/less severe) was tested using logistic regression with a covariate for *HTT* CAG repeat structure to account for non-canonical CAG repeats. In the continuous analysis, linear regression was used to test association of variants with residual age at motor onset, corrected for pure CAG lengths. Covariates used: principal components (PCA) 1-5; baseline variant rate (BVR); mean variant depth; study ID (Registry or Predict). Significance threshold = 1.3E-5 (Bonferroni correction for 3912 genes with at least 10 variants). No single gene reached this threshold.

Dichotomous (N=637)			Continuous (N=558)		
GO Term	Description	p	GO Term	Description	p
GO:0042578	phosphoric ester hydrolase activity	**9.66E-05**	GO:0006605	protein targeting	5.96E-03
GO:0006605	protein targeting	2.31E-04	GO:0001654	eye development	6.60E-03
GO:0051090	regulation of DNA binding transcription factor activity	3.16E-04	GO:0046982	protein heterodimerization activity	1.02E-02
GO:0009101	glycoprotein biosynthetic process	3.23E-04	GO:0043010	camera-type eye development	1.26E-02
GO:0050839	cell adhesion molecule binding	4.03E-04	GO:0051259	protein oligomerization	1.48E-02
GO:0009100	glycoprotein metabolic process	4.39E-04	GO:0010008	endosome membrane	1.49E-02
GO:0006511	ubiquitin-dependent protein catabolic process	6.23E-04	GO:0042578	modified amino acid binding	1.54E-02
GO:0019941	modification-dependent protein catabolic process	6.40E-04	GO:0006898	phosphoric ester hydrolase activity	1.61E-02
GO:0004842	ubiquitin-protein transferase activity	6.46E-04	GO:0072341	receptor-mediated endocytosis	1.95E-02
GO:0019787	ubiquitin-like protein transferase activity	7.05E-04	GO:0044440	endosomal part	2.87E-02
GO:0031406	carboxylic acid binding	1.03E-03	GO:0002250	adaptive immune response	3.41E-02
GO:0006935	chemotaxis	1.15E-03	GO:0098609	cell-cell adhesion	3.99E-02
GO:0050711	negative regulation of interleukin-1 secretion	1.16E-03	GO:0034138	negative regulation of interleukin-1 secretion	4.12E-02
GO:0006281	DNA repair	1.23E-03	GO:0031901	toll-like receptor 3 signaling pathway	5.08E-02
GO:0043177	organic acid binding	1.29E-03	GO:0050711	early endosome membrane	5.35E-02
GO:0061564	axon development	1.36E-03	GO:0097193	negative regulation of protein secretion	6.24E-02
GO:0042330	taxis	1.40E-03	GO:0050709	negative regulation of protein transport	6.51E-02
GO:0045088	regulation of innate immune response	1.67E-03	GO:0051224	intrinsic apoptotic signaling pathway	6.65E-02
GO:0051186	cofactor metabolic process	1.77E-03	GO:0001673	male germ cell nucleus	7.21E-02
GO:0035239	tube morphogenesis	2.06E-03	GO:0051962	positive regulation of nervous system development	8.02E-02

Supplementary Table 8: Association of candidate genetic pathways with HD phenotype in both dichotomous and continuous groups

Significant gene pathways from GeM-HD GWAS[5] (q<0.001) were selected as candidate pathways (N=233), and gene set membership was taken from the gene ontology (GO) database[6,7]. p values from corrected whole-exome SKAT-O analyses (see also Table S7) were combined across GO pathways and tested for association with HD phenotype using Fisher's combined probability test. Missing genes or genes with missing p values were excluded. Significance threshold = 1.1E-04 (Bonferroni correction for 233 pathways and 2 groups). Significant p-value in bold.

Name	Use/Target	Sequence
FAN1_Frag2F	Sanger (R377W; L395P)	AGGCAAAATCTCATAGTTCTGCA
FAN1_Frag2R	Sanger (R377W; L395P)	CATCATGCCCCAATCAGAGC
FAN1_Seq2F	Sanger (R377W; L395P)	CAATGATATCCCTCACAGC
FAN1_Seq2R	Sanger (R377W; L395P)	TGAAAACAAACACGTGCG
FAN1_Frag3F	Sanger (D498N; R507H; R507C)	ACTCCTTTCTGCTCCTGAACT
FAN1_Frag3R	Sanger (D498N; R507H; R507C)	CCAGCCTTCTCAATCTAACTACA
FAN1_Seq3F	Sanger (D498N; R507H; R507C)	TCCTTTCTGCTCCTGAAC
FAN1_Seq3R	Sanger (D498N; R507H; R507C)	CCAGCCTTCTCAATCTAAC
FAN1_Frag4F	Sanger (P654L; R658W)	TGGTAGCTGGCTGTGAGAAT
FAN1_Frag4R	Sanger (P654L; R658W)	TCACATGTTTAACGCCATCACA
FAN1_Seq4F	Sanger (P654L; R658W)	TAGCTGGCTGTGAGAATG
FAN1_Seq4R	Sanger (P654L; R658W)	TGTTTAACGCCATCACATC
FAN1_Frag6F	Sanger (K794R)	ACTTTGTGGTAAGGGAGGTCA
FAN1_Frag6R	Sanger (K794R)	CTGGGTGCCACAAGAGAAAG
FAN1_Seq6F	Sanger (K794R)	CTTTTGCTGACCTGAGGC
FAN1_Seq6R	Sanger (K794R)	CCACAAGAGAAAGCCTGC
FAN1_Frag7F	Sanger (V963Wins964L; R969L)	CCATTCTCTGTCACGAGGGA
FAN1_Frag7R	Sanger (V963Wins964L; R969L)	CGGCCCAAAAGCTCTCAAG
FAN1_Seq7F	Sanger (V963Wins964L; R969L)	CGAGGGAAGTGGCTAAC
FAN1_Seq7R	Sanger (V963Wins964L; R969L)	CCTACTTGTGGCCTCTG
FAN1_Frag8F	Sanger (D702E; Q717R)	CAGTGAGAGAGCAGAAGAGC
FAN1_Frag8R	Sanger (D702E; Q717R)	TGGGTGACAGAGCGAGACT
FAN1_Seq8F	Sanger (D702E; Q717R)	AGTGAGAGAGCAGAAGAG
FAN1_Seq8R	Sanger (D702E; Q717R)	ACCAAATATCCCCAATTCC
FAN1_Frag10F	Sanger (R982C; C1004G)	CAGTGAGAGAGCAGAAGAGC
FAN1_Frag10R	Sanger (R982C; C1004G)	ACTGTGTGGAATCAATGAGTGT
FAN1_Seq10F	Sanger (R982C; C1004G)	AGTGAGAGAGCAGAAGAG
FAN1_Seq10R	Sanger (R982C; C1004G)	TGTGTGGAATCAATGAGTG
FAN1_Frag12F	Sanger (M50R; V77I)	TCAGAGTTCGCTTTTCCCCT
FAN1_Frag12R	Sanger (M50R; V77I)	CACACTACGATTTCTCAGCTCA
FAN1_Seq12F	Sanger (M50R; V77I)	ACTCATGATGTCAGAAGGG
FAN1_Seq12R	Sanger (M50R; V77I)	TTGCTGAATCACTTTGGC
FAN1_Frag13F	Sanger (T187fs)	GGGAAGTAAAGCAGAAGATCAGT
FAN1_Frag13R	Sanger (T187fs)	TTCTCACATTCCCGGGTAGC
FAN1_Seq13F	Sanger (T187fs)	GCTGAGAAATCGTAGTGTG
FAN1_Seq13R	Sanger (T187fs)	GTTCAGGAATGCACTCTTC
FAM-huHTT-exon 1 F	Capillary electrophoresis *HTT* CAG	FAM-ATGAAGGCCTTCGAGTCCCTCAAGTCCTTC
huHTT-exon 1 R	Capillary electrophoresis *HTT* CAG	GGCGGCTGAGGAAGCTGAGGA
TOM112	This paper, based on [8]	TTTTTGTCTGAATCTGGTGCTGGGATCCAACATGTTCTAAC
TOM117	This paper, based on [8]	GTTAGAACATGTTGGATCCCAGCACCAGATTCAGACCTGATGACCGATCGTACGTTCGCTGCTG GCTACTGC
TOM122	This paper, based on [8]	GCAGTAGCCAGCAGCGAACGTACGATCGGTCATCAG
FAN1 KO gRNA1	gRNA *FAN1* exon 2: FAN1 knock-out	CTGATTGATAAGCTTCTACGAGG
FAN1 KO gRNA2	gRNA *FAN1* exon 2: FAN1 knock-out	GCACCATTTTACTGCAAACGGGG

FAN1 D960A gRNA	gRNA *FAN1* exon 13: D960A variant	AGGGGGCCTCCCCGACCTGGTGG
FAN1 D960A repair	D960A repair template	GTGCTCAGTGGTGTGTGCAGGCACCTGGCTGCTGACTTTCGACA CTGTCGAGGaGGCCTCCCCGcCCTGGTcGTGTGGAACTCCCAGA GCCGTCACTTTAAGGTCAGTTGAGGCAGAATGGA
FAN1-KO F	*FAN1* KO check	CCTGTGTTTTATTGCTCAGAACA
FAN1-KO R	*FAN1* KO check	CATTTCATCAAGGTGCCGGT
D960A FauI/StuI F	FAN1 D960A check	TCACGAGGGAAGTGGCTAAC
D960A FauI R	FAN1 D960A check	GCCAACAGCCACTCAAGAAATG
D960A StuI R	FAN1 D960A check	CACAGAATACAGCAGGAGTGATG

Supplementary Table 9: Oligonucleotides used in this study

Primers marked by 'Sanger' were used for sanger sequencing of *FAN1* variants in select individuals. *FAN1* Q717R was confirmed both by exome QC and Sanger sequencing to not exist (this was originally called but later refuted in the QC pipeline).

REAGENT	SOURCE	IDENTIFIER
Antibodies		
Anti-FAN1 (sheep polyclonal, second bleed)	CHDI	CHDI
Anti-β-Tubulin Antibody, clone AA2	Upstate	Cat#05-661 Lot#22237
Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor Plus 680	Invitrogen	Cat#A32788
IRDye® 800CW Donkey anti-Goat IgG Secondary Antibody	LI-COR	Cat#926-32214 Lot#C80717-07
Anti-OCT4 antibody	AbCam	Cat#ab19857
Anti-MAP2 antibody	AbCam	Cat#ab32454
Anti-CTIP2 antibody	AbCam	Cat#ab18465
Alexa Fluor goat anti-mouse IgG 488	Invitrogen	Cat#A11001
Alexa Fluor goat anti-rabbit IgG 568	Invitrogen	Cat#A11011
Biological Samples		
Genomic DNA from lymphoblastoid cell lines derived from HD patients in Registry study	CHDI	EHDN projects 0791 and 0803
Chemicals		
Essential 8 Flex Medium Kit	Life Technologies	Cat#A2858501
Advanced DMEM/F-12	Life Technologies	Cat#12634028
Knockout DMEM/F-12	Life Technologies	Cat#12660012
Neurobasal™ Medium	Life Technologies	Cat#21103049
Corning® Matrigel® Growth Factor Reduced (GFR) Basement Membrane Matrix, LDEV-free	BD Biosciences	Cat#354230
Poly-D-Lysine hyrobromide	Sigma-Aldrich	Cat#P6407
GlutaMAX	Thermo Fisher	Cat#35050-038
Penicillin/ Streptomycin (5000U/5000 µg)	Gibco	Cat#15070063
MACS NeuroBrew-21	Miltenyi	Cat#130-093-566
MACS NeuroBrew-21 (w/o Vitamin A)	Miltenyi	Cat#130-097-263
StemMACS™ IWR-1-endo	Miltenyi	Cat#130-110-491
Human BDNF, research grade	Miltenyi	Cat#130-096-286

StemMACS™ SB431542	Miltenyi	Cat#130-105-336
LDN -193189	StemGent	Cat#04-0019
Recombinant Human/Murine/Rat Activin A (Insect derived)	PeproTech	Cat#120-14
CHIR 99021	Bio-Techne	Cat#4423
PD0332991	Bio-Techne	Cat#4786
DAPT	Bio-Techne	Cat#2634
LM22A4	Bio-Techne	Cat#4607
Forskolin	Bio-Techne	Cat#1099
Ascorbic Acid	Sigma-Aldrich	Cat#A4544
Calcium Chloride	Sigma-Aldrich	Cat#499609-1G
γ-Aminobutyric acid (GABA)	Bio-Techne	Cat#0344
Y-27632 dihydrochloride (ROCK inhibitor)	Tocris	Cat#1254
ReLeSR	Stem Cell Technologies	Cat#05873
StemPro Accutase Cell Dissociation Reagent	Life Technologies	Cat#A1110501
Gentle Cell Dissociation Reagent	Stem Cell Technologies	Cat#07174
Hoechst 33342	Life Technologies	Cat#62249
TaKaRa LA Taq® DNA Polymerase with GC Buffer	Takara	Cat#RR02AG
Taq polyermase	Sigma-Aldrich	Cat#D4545
Custom 10X mix for PCR	Thermo Scientific [9]	Cat#SM-0005
AMPure XP SPRI beads	Beckman Coulter	Cat#A63881
OneTaq Hot Start DNA Polymerase	NEB	Cat#M0481L
FauI	NEB	Cat#R0651S
StuI	NEB	Cat#R0187S
CutSmart Buffer	NEB	Cat#B7204S
Hi-Di™ Formamide	Applied Biosystems	Cat# 4440753
Duplex buffer	IDT	Cat#11-05-01-03
Alt-R S.p. Cas9 nuclease, v.3	IDT	Cat# 1081058
cOmplete™, EDTA-free Protease Inhibitor Cocktail Tablets	Merck	Cat# 11873580001
Commercial Assays & Kits		
QIAamp DNA Mini Kit	QIAGEN	Cat#51306
QuickExtract DNA Extraction Solution	Cambio	Cat#QE09050
P3 Primary Cell 4D-Nucleofector™ X Kit L	Lonza	Cat#V4XP-3024
QIAquick PCR Purification Kit	QIAGEN	Cat#28104
MyTaq™	Bioline	Cat#BIO21127
Quant-iT™ PicoGreen™	ThermoFisher	Cat#P7589
TruSeq Rapid Exome Kit	Illumina	Cat#20020617
High sensitivity DNA chip for Bioanalyser	Agilent	Cat#5067-4626
HiSeq 3000/4000 PE Cluster Kit	Illumina	Cat#PE-410-1001
HiSeq 3000/4000 SBS kit (150 cycles)	Illumina	Cat#FC-410-1002
MiSeq Reagent Kit v3 (600-cycle)	Illumina	Cat#MS-102-3003
GeneScan™ 600 LIZ™ dye Size Standard v2.0	Applied Biosystems	Cat# 4408399
Databases		
dbNSFP	[2,3]	4.0
gnomAD	[4]	2.1.1
PREDICT-HD exomes	Genetic Modifiers of Huntington's Disease	**dbGaP Study Accession:** phs000371.v2.p1

REGISTRY-HD	http://www.ehdn.org/; [10]	R3 Cut
Cell Lines		
Human: HD iPSC lines (Q109N1, Q109N5)	[11]	
N1-FAN1$^{-/-}$ iPSC lines	This paper	N/A
N5-FAN1$^{-/-}$ iPSC lines	This paper	N/A
N5-FAN1$^{D960A/D960A}$ iPSC lines	This paper	N/A
N5-FAN1$^{D960A/WT}$ iPSC lines	This paper	N/A
Lymphoblastoid cell lines	CHDI	EHDN projects 0791 and 0803
Commercial Oligonucleotides		
Alt-R® CRISPR-Cas9 tracrRNA, ATTO™ 550	IDT	Cat#1075928
Software and Algorithms		
Burrows-Wheeler Aligner (BWA)	[12]	0.7.5a
Fragman software	CRAN.R-project.org/package=Fragman	1.0.9
GeneMapper Software	Applied Biosystems	4.1
Genome analysis toolkit (GATK)	[13–15]	3.6-0-g89b7209
GraphPad Prism	GraphPad Software, https://www.graphpad.com/scientific-software/prism/	8.2.1
Hail	https://github.com/hail-is/	0.1-5a67787
Peddy	[1]	0.3.5
Picard (picard-tools)	https://github.com/broadinstitute/picard/	1.97
Primer3	[16,17]	Accessed June 2020
R	https://www.r-project.org/	3.6.0
SAMtools	[18,19]	1.9
Scale-HD	https://github.com/helloabunai/ScaleHD/	0.322
Tablet	[20]	1.19.05.28
UCSC In-Silico PCR	https://genome.ucsc.edu/cgi-bin/hgPcr	Accessed June 2020
Variant-effect predictor tool (VEP)	[21]	95
VerifyBamID	[22]	1.1.3

Supplementary Table 10: Reagents used in this study

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Source Data for Supplementary Figures

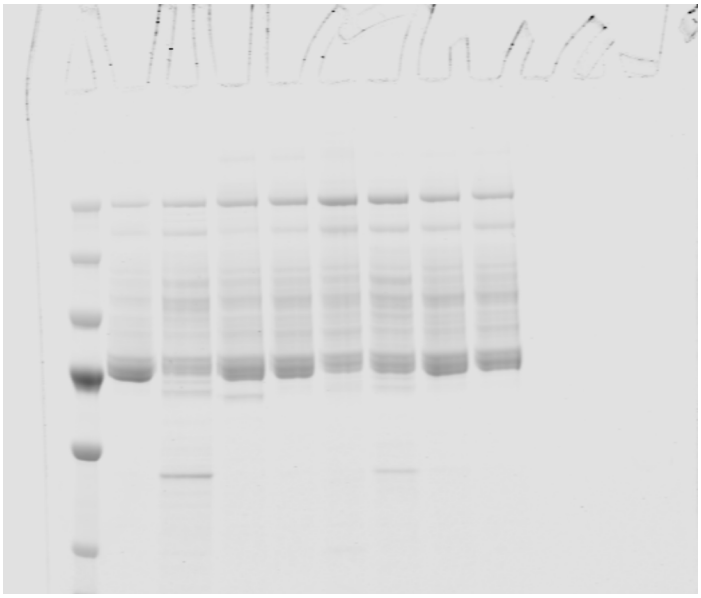

Fig. 3b. 4-12% Bis-Tris SDS-PAGE stained with Coomassie blue

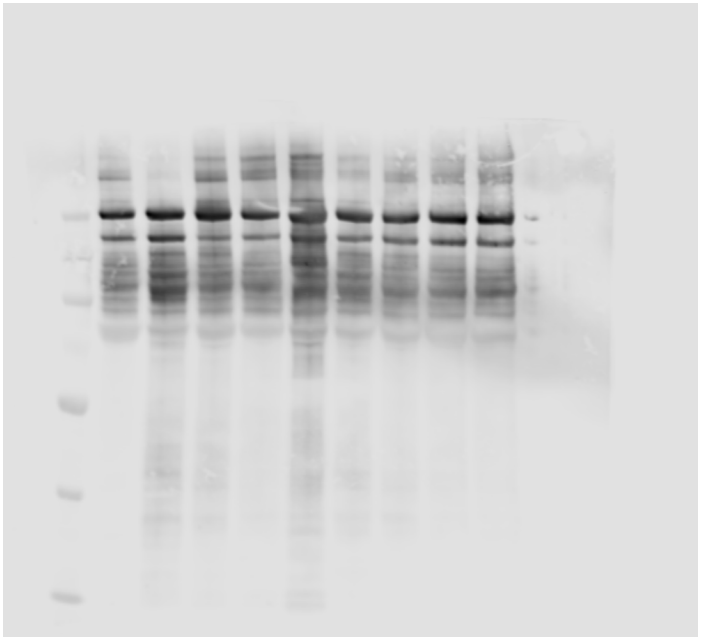

Fig. 3c. 4-12% Bis-Tris SDS-PAGE. Immunoblotted with anti-FAN1 sheep polyclonal antibody

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