

Supplementary Materials for

Histone H3.3 beyond cancer: Germline mutations in *Histone 3 Family 3A and 3B* cause a previously unidentified neurodegenerative disorder in 46 patients

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Other Supplementary Material for this manuscript includes the following:

(available at advances.sciencemag.org/cgi/content/full/6/49/eabc9207/DC1)

Table S1

Supplementary Materials

Supplemental Authors Groups:

1) Care for Rare: The project was selected for analysis by the Care4Rare Consortium Gene Discovery Steering Committee consisting of Kym Boycott (lead; University of Ottawa), Alex MacKenzie (co-lead; University of Ottawa), Jacek Majewski (McGill University), Michael Brudno (University of Toronto), Dennis Bulman (University of Ottawa) and David Dymant (University of Ottawa).

2) CAUSES study: Investigators in the CAUSES Study (Clinical Assessment of the Utility of Sequencing as a Service) include Shelin Adam, Christèle du Souich, Alison M. Elliott, Anna Lehman, Jill Mwenifumbo, Tanya N. Nelson, Clara van Karnebeek, and Jan M. Friedman (PI). The bioinformatic pipeline used in part of the CAUSES study was developed in the laboratory of Wyeth Wasserman. The CAUSES project is funded by the Mining for Miracles (BCCH Foundation) and Genome British Columbia, with support from the British Columbia Provincial Health Services Authority and British Columbia Women's Hospital.

3) DDD study: The DDD study presents independent research commissioned by the Health Innovation Challenge Fund [grant number HICF-1009-003]. This study makes use of DECIPHER (<http://decipher.sanger.ac.uk>), which is funded by Wellcome. See Nature PMID: 25533962 or www.ddduk.org/access.html for full acknowledgement.

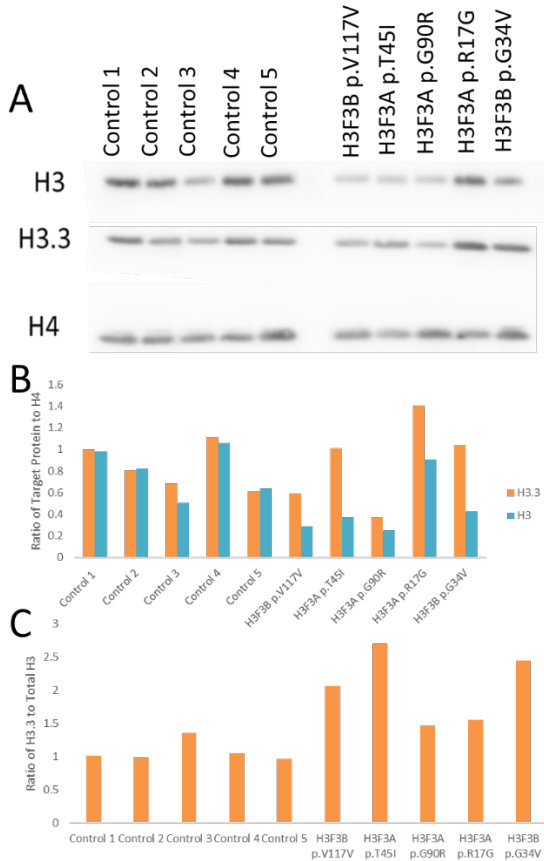
4) UDN study: Patrick Allard, UCLA Institute for Society & Genetics; Hayk Barseghyan, Center for Genetic Medicine Research, Children's National Medical Center, Washington, DC; Manish J. Butte, Department of Pediatrics/Division of Immunology, Allergy, and Rheumatology; Department of Microbiology, Immunology, and Molecular Genetics; Esteban C. Dell'Angelica Department of Human Genetics, David Geffen School of Medicine at UCLA; Katrina M. Dipple University of Washington Department of Pediatrics, Division of Genetic Medicine; UCLA Departments of Human Genetics and Pediatrics, David Geffen School of Medicine, UCLA; Naghmeh Dorrani, Department of Pediatrics David Geffen School of Medicine at UCLA; Emilie D. Douine Department of Human Genetics, David Geffen School of Medicine, UCLA; Ascia Eskin Department of Human Genetics, David Geffen School of Medicine, UCLA; Brent L. Fogel Departments of Neurology and Human Genetics, David Geffen School of Medicine, UCLA; Matthew R. Herzog Department of Human Genetics, David Geffen School of Medicine, UCLA; Hane Lee Pathology and Laboratory Medicine, David Geffen School of Medicine, UCLA; Sandra K. Loo Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavior, David Geffen School of Medicine, UCLA; Martin G. Martin Department of Pediatrics, Division of Gastroenterology and Nutrition, Mattel Children's Hospital; Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research and the David Geffen School of Medicine, UCLA; Julian A. Martínez-Agosto Department of Human Genetic; Division of Medical Genetics, Department of Pediatrics, David Geffen School of Medicine, UCLA; Stan F. Nelson Department of Human Genetics; Department of Pathology and Laboratory Medicine, David Geffen School of Medicine; Christina GS. Palmer Department of Psychiatry & Biobehavioral Sciences, Department of Human Genetics, Institute for Society & Genetics, David Geffen School of Medicine, UCLA; Jeanette C. Papp Department

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S. Fig. 1. Patient facial features: Although the patients are not strikingly dysmorphic, they share some features that include a broad forehead, high insertion of the columella, and deep-set almond-shaped eyes with short palpebral fissures. Photo Credits: Amy Pizzino, Children's Hospital of Philadelphia; Sarah Joy Dean, University of Alabama; Davor Lessel, University Medical Center Hamburg-Eppendorf; Constance T.R.M. Stumpel, Maastricht University Medical Center; Claudia Catarino, Ludwig-Maximilians University; Sandra Mercier, CHU Nantes; Michael J. Lyons, Greenwood Genetics Center; Julian A. Martinez-Agosto, David Geffen School of Medicine, UCLA; Elliott Sherr, UCSF; Elly Brokamp, Vanderbilt University; Katrin Õunap, Tartu University Hospital; Francesca Clementina Radio, Ospedale Pediatrico Bambino Gesù; Nina Powell-Hamilton, Alfred I. duPont Hospital for Children; K.E. Stuurman, Erasmus University Medical Center; Theresa Grebe, Phoenix Children's Hospital.

S. Table 1. Extended phenotypic information for 46 patients with mutations in H3F3A or H3F3B



S. Fig 2. Quantification of H3 and H3.3 protein in patients and control fibroblasts: Western blot quantification of total H3 and H3.3 in five control and five patient samples. There is a significant difference in the ratio of H3.3 to total H3 in the patient samples compared to controls, students T-test two-tailed $p < 0.0049$.

Subject ID	EB257-01a	EB256-01a	EB252-01a	Control 1	Control 2	Control 3
Mutation	H3F3A p.T45I	H3F3A p.G90R	H3F3A p.R16G	NA	NA	NA
Gene	FPKM	FPKM	FPKM	FPKM	FPKM	FPKM
HIST1H3B	31.93	69.93	12.77	19.98	9.62	8.36
H3F3B	186.82	143.24	96.12	161.48	146.50	169.74
H3F3A	29.23	18.09	17.00	18.36	17.85	21.94
HIST1H3I	9.90	15.91	4.29	9.45	2.13	5.58
HIST2H3D	1.17	0.10	0.00	0.70	0.00	0.44
HIST1H3C	20.89	19.12	4.60	18.28	4.60	5.32
HIST1H3E	10.78	14.43	2.61	2.71	2.56	5.00
HIST1H3J	6.09	12.58	3.12	6.39	2.95	3.62
HIST1H3D	14.06	4.75	1.50	12.94	3.42	5.85
HIST1H3A	8.89	5.84	2.47	11.86	2.51	7.16
HIST2H3C	0.06	0.00	0.00	0.08	0.00	0.00
HIST1H3H	11.53	6.91	2.08	9.45	2.37	4.03

HIST2H3A	0.03	0.06	0.02	0.05	0.02	0.00
HIST1H3G	13.55	29.68	4.87	6.49	3.62	7.02
HIST1H3F	14.15	17.33	4.33	2.56	3.08	3.75
H3.3 expression in H3	0.6017	0.4507	0.7262	0.6405	0.8168	0.7735

S. Table 2. H3.3 expression representation of all histone H3 in transformed lymphoblastoid cells

Gene	FPKM_Cases	FPKM_Controls	log2(FPKM_Cases/FPKM_Controls)	Test Stat	p value	q value
ABCB4	2.71579	1.02221	-1.40968	-1.0813	0.03355	0.871071
MYLIP	10.7263	3.0545	-1.81215	-1.80005	0.00195	0.164984
IL32	3.21925	1.46191	-1.13888	-0.825863	0.0329	0.860765
CD9	14.21	5.89882	-1.26841	-1.34747	0.01855	0.635595
ANLN	14.6791	7.20536	-1.02662	-0.867304	0.02145	0.686966
FHL1	212.104	100.136	-1.08281	-1.6478	0.0018	0.161109
TNC	963.341	256.032	-1.91173	-1.06951	0.0061	0.335717
CELF2	11.0801	3.03405	-1.86865	-1.50379	0.00915	0.431006
NEDD4L	6.80875	2.4604	-1.4685	-0.763326	0.00785	0.388073
PTGER3	8.63915	1.36988	-2.65684	-2.02794	0.0008	0.0958085
SYNE2	2.78524	1.27303	-1.12954	-0.641461	0.00725	0.366945
CDON	37.5176	11.4165	-1.71644	-1.44337	0.00655	0.350281
NTN1	19.4924	1.29198	-3.91525	-3.17147	0.0003	0.04638
TLE2	3.23608	1.14756	-1.49567	-0.993557	0.01055	0.467222
ASPM	4.19224	1.28976	-1.70063	-2.34758	5.00E-05	0.0111882
HMMR	3.73086	1.33873	-1.47864	-1.2091	0.021	0.678311
NOTCH3	6.54555	2.23461	-1.5505	-0.998776	0.00665	0.352305
MCM6	7.59809	3.65229	-1.05684	-1.32492	0.0092	0.431006
FBLN1	256.156	39.9361	-2.68126	-2.69787	5.00E-05	0.0111882
ITGA8	46.4024	6.65272	-2.80218	-2.76786	5.00E-05	0.0111882
BRINP1	13.392	3.14911	-2.08835	-1.87605	0.0041	0.267144
SLC1A3	17.2332	7.34608	-1.23015	-0.847702	0.03455	0.890238
NDC80	4.16526	1.21052	-1.78278	-1.62533	0.00295	0.214392
MEF2C	7.70317	2.33582	-1.72152	-1.09209	0.0287	0.80275
SERTAD4	10.9564	4.02799	-1.44364	-1.23633	0.0383	0.933137
NID2	39.4993	17.2663	-1.19387	-1.14355	0.01665	0.599894
AURKA	6.72006	3.27488	-1.03703	-1.15701	0.04555	1
TPX2	7.87155	3.10473	-1.34218	-1.76257	0.00215	0.17749
ARHGAP28	11.5165	2.24286	-2.3603	-0.577127	0.0343	0.886483
ORC6	3.63964	1.16949	-1.63792	-1.46913	0.01615	0.590638
CDC6	3.37334	1.25289	-1.42892	-1.08608	0.01155	0.487393
SCD	17.111	6.66995	-1.35917	-2.20422	0.0002	0.0333451
PALM	8.77024	2.16754	-2.01656	-1.74363	0.00125	0.128833
CDKN3	7.51512	2.95257	-1.34782	-1.16245	0.044	0.992765
DOK5	6.53522	1.59281	-2.03666	-0.954766	0.0384	0.934235

MXRA5	126.27	33.4057	-1.91834	-2.77899	5.00E-05	0.0111882
FGF9	6.75797	2.24504	-1.58985	-1.27208	0.0111	0.475483
CEP152	2.66497	1.10557	-1.26933	-0.618197	0.049	1
SFRP1	38.6713	10.2926	-1.90966	-2.19175	0.0004	0.0581402
OLFM2	32.6351	5.06997	-2.68637	-1.98541	0.0073	0.368379
EPHB6	3.53586	1.1329	-1.64204	-1.03866	0.0211	0.678311
EZH2	3.42949	1.26279	-1.44137	-1.01979	0.04415	0.992765
CXCL12	118.717	39.9319	-1.57191	-2.55198	5.00E-05	0.0111882
SOD3	5.7173	1.69646	-1.7528	-1.64589	0.00965	0.442339
KLF3	12.5286	5.4837	-1.192	-1.68168	0.00165	0.151675
SLC38A1	33.757	15.6398	-1.10996	-1.37605	0.00545	0.312063
GPR133	17.3579	7.51292	-1.20815	-1.00944	0.03	0.820225
FBXO5	3.65013	1.74848	-1.06185	-1.16615	0.04265	0.984133
SMOC2	48.7471	1.01311	-5.58845	-3.02392	0.0235	0.711105
LMNB1	13.4172	4.11856	-1.70387	-1.4586	0.01705	0.606595
SMC4	26.7178	8.91462	-1.58356	-0.92643	0.0047	0.288549
IGFBP2	138.103	2.5526	-5.75763	-5.09331	5.00E-05	0.0111882
IGFBP5	254.045	85.9025	-1.56431	-1.8381	0.00185	0.162171
PRRX1	96.6986	45.7216	-1.08062	-0.920956	0.0275	0.779442
CENPF	8.24794	2.72192	-1.59941	-1.55835	5.00E-05	0.0111882
HELLS	4.27855	1.7888	-1.25813	-0.975684	0.0429	0.984558
TMPO	33.4247	13.483	-1.30977	-1.37325	0.01835	0.635595
FMOD	30.2375	14.1558	-1.09495	-1.71319	0.00195	0.164984
HJURP	3.51118	1.21645	-1.52928	-1.2027	0.0194	0.652009
PTGIS	35.698	13.5732	-1.39508	-2.04214	0.00015	0.0265719
HIST1H1D	35.868	9.49785	-1.91702	-2.59476	5.00E-05	0.0111882
HIST1H3B	38.0082	12.4709	-1.60774	-1.94961	0.00155	0.14404
SOX4	9.88634	4.08245	-1.276	-2.03401	0.0005	0.068024
MYH2	6.81674	1.04845	-2.70083	-2.09476	0.002	0.167547
SLC25A23	6.42945	2.96757	-1.11541	-1.07541	0.02555	0.74021
SIX1	4.46554	1.48669	-1.58673	-1.10534	0.04225	0.981383
DLGAP5	4.92113	1.53483	-1.68092	-1.75201	0.0022	0.179011
AKAP12	47.3882	6.8142	-2.79791	-4.01287	5.00E-05	0.0111882
TOP2A	12.6753	3.96866	-1.6753	-2.23517	5.00E-05	0.0111882
EMILIN2	11.8188	4.84944	-1.28519	-1.79637	0.00285	0.210727
MYH10	33.9825	10.5738	-1.6843	-1.24831	0.0001	0.0195471
DCLK1	6.3207	1.21938	-2.37394	-1.54032	0.0078	0.387856
IL15RA	5.71876	1.25084	-2.19281	-1.69275	0.0005	0.068024
SLC43A3	8.55979	4.08807	-1.06616	-1.06694	0.00525	0.304715
ANKRD6	3.41412	1.03652	-1.71977	-0.713878	0.0304	0.821912
PLXNC1	8.86646	2.443	-1.85971	-1.40006	0.0019	0.164854
NOV	29.8702	10.2686	-1.54046	-2.01468	0.0006	0.0761463
NUSAP1	13.184	3.95132	-1.73838	-1.61202	0.0033	0.227206
KIF11	3.86946	1.34121	-1.5286	-1.91725	0.0014	0.135275
CEP55	7.54321	2.26968	-1.73269	-1.72365	0.00175	0.158301

TET1	3.14577	1.38673	-1.18173	-1.33645	0.02335	0.707825
SLC40A1	5.94987	1.7061	-1.80215	-1.78014	5.00E-05	0.0111882
CENPE	3.34246	1.54065	-1.11737	-0.79187	0.0211	0.678311
SLC39A8	5.11259	1.68399	-1.60217	-0.977014	0.04655	1
HAPLN3	10.4627	4.62702	-1.1771	-1.38404	0.02455	0.731377
ABCA8	10.7182	1.90968	-2.48866	-1.90225	5.00E-05	0.0111882
SECTM1	41.8511	15.6308	-1.42087	-1.39579	0.0135	0.531438
DPT ARHGAP2 6	387.81 9.43354	56.677 3.62201	-2.77451 -1.38101	-3.32539 -0.467542	5.00E-05 0.0247	0.0111882 0.731791
SERPING1	20.0585	9.38743	-1.09541	-1.35148	0.0228	0.698625
SESN3	6.69791	1.85774	-1.85016	-1.73487	0.0001	0.0195471
AKR1C2	50.2423	18.3644	-1.45199	-1.59519	0.02065	0.671461
ABCA9	5.42894	1.69408	-1.68017	-1.09697	0.00145	0.138532
GDF6	4.75352	1.8565	-1.35641	-1.674	0.0049	0.296272
BUB1B	3.63138	1.51911	-1.25729	-0.921916	0.0197	0.656898
C1R	658.134	222.25	-1.5662	-1.76321	0.01215	0.503958
PPAP2B	282.763	137.683	-1.03825	-0.987513	0.04935	1
OLFML2B	14.786	4.09312	-1.85296	-1.59081	0.003	0.217098
SPRY1	12.1777	1.63366	-2.89807	-2.89985	5.00E-05	0.0111882
ERAP2	9.30427	1.14452	-3.02316	-0.887727	0.0153	0.574375
PTTG1 KIAA1324 L	19.5221 28.273	9.52055 5.23446	-1.03599 -2.43331	-1.29355 -1.66594	0.0259 0.00065	0.747802 0.0801007
PHKG1	6.14365	1.45917	-2.07394	-1.32352	0.01225	0.504033
OSR2	30.6459	9.91683	-1.62775	-1.78905	0.01055	0.467222
CTHRC1	77.9178	36.7154	-1.08557	-1.66612	0.0024	0.190721
ABCA1	19.023	5.55645	-1.77551	-1.85249	0.0011	0.119914
SVEP1	73.2728	17.7031	-2.04928	-2.4713	0.0001	0.0195471
C10orf10	37.5148	7.81415	-2.2633	-2.58742	0.0004	0.0581402
DACT1	18.8669	5.88129	-1.68165	-2.04622	0.00015	0.0265719
VSTM4	32.4559	8.29975	-1.96734	-2.53206	0.0003	0.04638
MFAP4	86.4948	31.7093	-1.44771	-2.29694	5.00E-05	0.0111882
PLK1	3.6376	1.27442	-1.51314	-1.14882	0.01545	0.577456
TNXB	17.5193	5.11974	-1.7748	-1.76542	0.031	0.830246
TM4SF20	4.06696	1.11666	-1.86477	-1.39583	0.007	0.362933
BUB1	4.6818	2.04894	-1.19218	-1.05789	0.01605	0.589517
CDK1	6.32417	2.05579	-1.62118	-1.61787	0.0015	0.140934
PDGFD	51.7081	15.1145	-1.77446	-1.67537	0.0032	0.224873
SHCBP1	3.24326	1.16799	-1.47342	-1.10359	0.00415	0.268346
RRM2	9.46553	1.84715	-2.35738	-1.96111	5.00E-05	0.0111882
ID4	12.0953	5.93406	-1.02736	-1.36767	0.02205	0.690869
PODN	41.5325	19.7258	-1.07415	-1.36162	0.01665	0.599894
UBE2C MARCKSL 1	8.24535 4.00351	3.11132 1.6819	-1.40606 -1.25117	-1.30736 -1.32467	0.0216 0.0184	0.689174 0.635595
MAF	2.85663	1.19995	-1.25134	-1.14991	0.02085	0.67667

RMI1	4.34801	1.5654	-1.47383	-1.39156	0.0218	0.690374
AURKB	2.98817	1.1776	-1.34342	-0.9925	0.02215	0.691161
CDC42EP4	9.68249	4.6437	-1.0601	-1.351	0.01435	0.549631
KCNA4	4.91449	1.64195	-1.58164	-1.0568	0.01865	0.635595
AP1S2	38.9648	16.2021	-1.26599	-1.27809	0.0176	0.622257
NDN	12.6343	1.66144	-2.92683	-3.2094	5.00E-05	0.0111882
IQGAP3	2.58405	1.06771	-1.27512	-1.37521	0.00935	0.436703
HIST1H1B	35.3672	16.1795	-1.12824	-1.58787	0.00705	0.36331
OLFML2A	3.29172	1.06199	-1.63206	-1.71665	0.00185	0.162171
COL14A1	10.5635	1.91587	-2.46302	-2.2406	0.00185	0.162171
COL4A5	9.9059	3.53191	-1.48784	-0.858739	0.0105	0.467222
APOD	10.2873	1.05477	-3.28586	-2.69264	0.0001	0.0195471
PLAC9	33.4639	10.694	-1.6458	-1.75645	0.00945	0.436703
HIST1H2B O	14.9054	5.49446	-1.43979	-1.49954	0.0109	0.475296
HIST1H2B M	8.10544	2.62633	-1.62584	-1.4442	0.0179	0.627644
MME	109.131	52.7323	-1.0493	-1.03282	0.02055	0.670774
ADH1B	10.4111	3.68612	-1.49795	-1.50956	0.02565	0.741843
HIST1H2A G	4.60773	2.20996	-1.06003	-1.28025	0.0284	0.798298
HIST1H3E HIST1H2B H	9.20726	3.36938	-1.45029	-1.31834	0.03025	0.821776
MFAP5	438.269	169.812	-1.36788	-1.4002	0.0033	0.227206
HIST1H2B F	3.6127	1.34821	-1.42203	-1.3791	0.0186	0.635595
MBP	10.2671	4.16351	-1.30216	-0.906753	0.02555	0.74021
HIST1H4F HIST1H2A L	18.2413	7.80628	-1.2245	-1.3244	0.0246	0.731377
PRC1	13.9259	6.22368	-1.16193	-1.29162	0.00195	0.164984
TGM2	7.69583	3.24958	-1.24382	-1.5598	0.0095	0.437824
CENPW CRHR1- IT1	5.84658	2.02791	-1.5276	-1.36371	0.0227	0.698625
RANBP17	11.9423	2.12939	-2.48757	-1.7866	5.00E-05	0.0111882
RANBP17	7.62502	3.13513	-1.28222	-0.596036	0.0364	0.908813
RNVU1-14	26.5967	9.28833	-1.51775	-1.2046	0.03605	0.908813
DIO2 RP11- 632K20.7	17.9267	1.56905	-3.51414	-1.85558	5.00E-05	0.0111882
MIR503HG RP11- 481H12.1	9.38727	2.38537	-1.97649	-1.12011	0.0206	0.671118
MIR503HG RP11- 481H12.1	11.5052	5.34632	-1.10567	-0.977593	0.03125	0.832974
KIFC1 hsa-mir- 6723	5.74143	1.89808	-1.59687	-1.22672	0.0486	1
KIFC1 hsa-mir- 6723	3.09675	1.02093	-1.60087	-1.25908	0.0085	0.413003
AQP1	11.8814	3.90207	-1.60639	-1.56855	0.0168	0.601475
AQP1	168.924	6.45651	-4.70947	-4.32398	0.00865	0.415542
SEPP1 RP11- 760H22.2	26.2142	6.87315	-1.93131	-1.81318	0.02365	0.714373
SEPP1 RP11- 760H22.2	4.63262	1.87826	-1.30243	-1.2103	0.004	0.261631
HIST1H3G	15.9485	5.62572	-1.50331	-1.57429	0.00785	0.388073

S. Table 3. Upregulated expression of genes in cases with at least 2-fold change in fibroblast cells

Supplemental Table 4. Enrichment analysis of upregulated genes in cases in fibroblast cells

GO Biological Process Term	Gene Count	Percentage	P Value	Benjamini-Hochberg Adjusted P Value
mitotic cell cycle process	40	0.2	2.30E-17	7.80E-14
mitotic cell cycle	41	0.2	6.10E-17	1.90E-13
mitotic nuclear division	25	0.1	5.20E-13	5.80E-10
cell division	28	0.1	8.90E-13	7.50E-10
cellular component organization	97	0.4	1.60E-12	1.00E-09
DNA packaging	18	0.1	3.20E-12	1.80E-09
mitotic cell cycle phase transition	26	0.1	3.20E-12	1.60E-09
cell cycle process	41	0.2	5.00E-12	2.10E-09
chromosome organization	38	0.2	7.10E-12	2.70E-09
cellular component organization or biogenesis	97	0.4	8.40E-12	2.80E-09
cell proliferation	48	0.2	9.40E-12	2.90E-09
cell cycle phase transition	26	0.1	1.20E-11	3.50E-09
mitotic sister chromatid segregation	15	0.1	2.80E-11	7.20E-09
nuclear division	26	0.1	4.90E-11	1.20E-08
DNA conformation change	19	0.1	6.40E-11	1.40E-08
chromosome segregation	20	0.1	1.20E-10	2.50E-08
organelle fission	26	0.1	1.90E-10	3.80E-08
cell cycle	43	0.2	2.10E-10	3.90E-08
regulation of mitotic nuclear division	14	0.1	3.10E-10	5.60E-08
sister chromatid segregation	16	0.1	1.30E-09	2.20E-07
regulation of mitotic cell cycle	22	0.1	2.10E-09	3.40E-07
regulation of nuclear division	14	0.1	2.20E-09	3.40E-07
protein-DNA complex assembly	16	0.1	2.50E-09	3.70E-07
chromatin assembly	14	0.1	2.80E-09	3.90E-07
nuclear chromosome segregation	17	0.1	5.00E-09	6.80E-07
regulation of mitotic metaphase/anaphase transition	9	0	7.10E-09	9.20E-07
regulation of metaphase/anaphase transition of cell cycle	9	0	8.40E-09	1.10E-06
nucleosome assembly	13	0.1	9.20E-09	1.10E-06
regulation of mitotic sister chromatid separation	9	0	1.00E-08	1.20E-06
protein-DNA complex subunit organization	16	0.1	1.10E-08	1.20E-06
metaphase/anaphase transition of cell cycle	9	0	1.20E-08	1.30E-06
mitotic sister chromatid separation	9	0	1.40E-08	1.50E-06
regulation of cell proliferation	38	0.2	1.40E-08	1.40E-06
chromatin assembly or disassembly	14	0.1	1.40E-08	1.40E-06
chromosome separation	10	0	1.50E-08	1.50E-06
regulation of mitotic cell cycle phase transition	17	0.1	1.60E-08	1.50E-06
positive regulation of cell proliferation	27	0.1	2.40E-08	2.20E-06
regulation of mitotic sister chromatid segregation	9	0	3.00E-08	2.70E-06
regulation of cell cycle phase transition	17	0.1	4.60E-08	4.00E-06
regulation of chromosome segregation	10	0	5.30E-08	4.40E-06
nucleosome organization	13	0.1	5.80E-08	4.80E-06
regulation of cell cycle process	22	0.1	6.00E-08	4.80E-06
negative regulation of biological process	72	0.3	8.60E-08	6.80E-06
G1/S transition of mitotic cell cycle	14	0.1	9.30E-08	7.10E-06
regulation of sister chromatid segregation	9	0	1.30E-07	9.50E-06
negative regulation of cellular process	68	0.3	1.60E-07	1.20E-05
cell cycle G1/S phase transition	14	0.1	2.50E-07	1.80E-05
positive regulation of biological process	77	0.3	3.60E-07	2.50E-05

negative regulation of mitotic cell cycle	13	0.1	5.50E-07	3.80E-05
cellular component assembly	48	0.2	6.40E-07	4.30E-05
developmental growth	20	0.1	9.10E-07	6.00E-05
negative regulation of mitotic cell cycle phase transition	11	0	1.10E-06	7.00E-05
single-organism organelle organization	35	0.2	1.10E-06	7.20E-05
negative regulation of cellular metabolic process	44	0.2	1.30E-06	8.30E-05
regulation of cell cycle	26	0.1	1.30E-06	8.20E-05
negative regulation of cell cycle process	13	0.1	1.50E-06	8.70E-05
growth	25	0.1	2.10E-06	1.20E-04
negative regulation of cell cycle phase transition	11	0	2.10E-06	1.20E-04
negative regulation of macromolecule metabolic process	43	0.2	2.80E-06	1.60E-04
negative regulation of gene expression, epigenetic	10	0	3.30E-06	1.80E-04
negative regulation of metabolic process	45	0.2	3.70E-06	2.00E-04
negative regulation of cell cycle	17	0.1	4.00E-06	2.20E-04
urogenital system development	14	0.1	5.20E-06	2.80E-04
negative regulation of transcription, DNA-templated	27	0.1	5.70E-06	3.00E-04
spindle organization	9	0	5.80E-06	3.00E-04
organelle organization	58	0.3	6.20E-06	3.20E-04
regulation of cellular component organization	42	0.2	6.80E-06	3.40E-04
cytoskeleton organization	27	0.1	7.20E-06	3.50E-04
extracellular matrix organization	14	0.1	8.30E-06	4.00E-04
extracellular structure organization	14	0.1	8.50E-06	4.10E-04
regulation of neuron differentiation	18	0.1	9.10E-06	4.30E-04
muscle cell proliferation	10	0	9.50E-06	4.40E-04
chromatin silencing	9	0	1.00E-05	4.80E-04
negative regulation of cellular macromolecule biosynthetic process	29	0.1	1.20E-05	5.30E-04
negative regulation of nucleic acid-templated transcription	27	0.1	1.20E-05	5.30E-04
negative regulation of cellular biosynthetic process	31	0.1	1.20E-05	5.40E-04
regulation of developmental process	39	0.2	1.30E-05	5.60E-04
cellular component biogenesis	48	0.2	1.30E-05	5.60E-04
chromatin organization	21	0.1	1.40E-05	5.80E-04
developmental growth involved in morphogenesis	11	0	1.40E-05	5.90E-04
spindle assembly	8	0	1.50E-05	6.00E-04
negative regulation of RNA biosynthetic process	27	0.1	1.50E-05	6.20E-04
negative regulation of biosynthetic process	31	0.1	1.70E-05	6.80E-04
negative regulation of nitrogen compound metabolic process	31	0.1	1.70E-05	6.90E-04
nervous system development	39	0.2	2.00E-05	7.80E-04
negative regulation of nucleobase-containing compound metabolic process	29	0.1	2.20E-05	8.60E-04
spindle checkpoint	6	0	2.20E-05	8.70E-04
neuron differentiation	27	0.1	2.40E-05	9.20E-04
cell adhesion	33	0.1	2.60E-05	9.90E-04
biological adhesion	33	0.1	2.80E-05	1.00E-03
cytoskeleton-dependent cytokinesis	6	0	2.90E-05	1.10E-03
negative regulation of RNA metabolic process	27	0.1	2.90E-05	1.10E-03
regulation of neurogenesis	19	0.1	3.20E-05	1.20E-03
protein heterotetramerization	6	0	3.30E-05	1.20E-03
metaphase/anaphase transition of mitotic cell cycle	6	0	3.30E-05	1.20E-03
negative regulation of gene expression	30	0.1	3.50E-05	1.20E-03
cell cycle checkpoint	11	0	3.60E-05	1.30E-03

negative regulation of macromolecule biosynthetic process	29	0.1	4.00E-05	1.40E-03
regulation of chromosome organization	12	0.1	5.00E-05	1.70E-03
generation of neurons	28	0.1	5.00E-05	1.70E-03
single-organism cellular process	129	0.6	5.80E-05	1.90E-03
neurogenesis	29	0.1	5.80E-05	1.90E-03
regulation of cell development	21	0.1	5.80E-05	1.90E-03
anaphase-promoting complex-dependent catabolic process	7	0	6.90E-05	2.30E-03
mitotic spindle assembly checkpoint	5	0	7.40E-05	2.40E-03
regulation of multicellular organismal process	43	0.2	7.50E-05	2.40E-03
mitotic cell cycle checkpoint	9	0	8.30E-05	2.60E-03
regulation of multicellular organismal development	32	0.1	8.40E-05	2.60E-03
spindle assembly checkpoint	5	0	8.70E-05	2.70E-03
single-multicellular organism process	76	0.3	9.20E-05	2.80E-03
cytokinesis	8	0	9.30E-05	2.80E-03
microtubule cytoskeleton organization	14	0.1	1.10E-04	3.30E-03
centromere complex assembly	6	0	1.10E-04	3.30E-03
cellular response to acid chemical	9	0	1.10E-04	3.30E-03
tissue development	32	0.1	1.20E-04	3.60E-03
positive regulation of cellular process	64	0.3	1.30E-04	3.70E-03
kidney development	11	0	1.30E-04	3.80E-03
negative regulation of nuclear division	6	0	1.30E-04	3.80E-03
regulation of nervous system development	19	0.1	1.50E-04	4.20E-03
protein ubiquitination involved in ubiquitin-dependent protein catabolic process	10	0	1.60E-04	4.40E-03
organ morphogenesis	22	0.1	1.60E-04	4.60E-03
multicellular organismal process	85	0.4	1.70E-04	4.80E-03
DNA replication-dependent nucleosome organization	5	0	1.70E-04	4.70E-03
DNA replication-dependent nucleosome assembly	5	0	1.70E-04	4.70E-03
regulation of cell differentiation	29	0.1	1.80E-04	4.80E-03
response to acid chemical	11	0	1.80E-04	4.90E-03
protein localization to chromosome	6	0	1.80E-04	4.90E-03
cellular macromolecular complex assembly	22	0.1	1.90E-04	5.20E-03
mitotic cytokinesis	5	0	1.90E-04	5.10E-03
mitotic spindle checkpoint	5	0	1.90E-04	5.10E-03
negative regulation of mitotic sister chromatid separation	5	0	1.90E-04	5.10E-03
negative regulation of mitotic metaphase/anaphase transition	5	0	1.90E-04	5.10E-03
response to wounding	17	0.1	2.00E-04	5.20E-03
renal system development	11	0	2.10E-04	5.40E-03
negative regulation of metaphase/anaphase transition of cell cycle	5	0	2.20E-04	5.70E-03
kinetochore organization	4	0	2.30E-04	5.80E-03
regulation of biological quality	51	0.2	2.30E-04	5.90E-03
negative regulation of mitotic sister chromatid segregation	5	0	2.50E-04	6.20E-03
neuron projection extension	8	0	2.50E-04	6.30E-03
anatomical structure morphogenesis	41	0.2	2.70E-04	6.80E-03
single-organism process	135	0.6	2.80E-04	6.90E-03
protein complex subunit organization	30	0.1	2.90E-04	7.10E-03
macromolecular complex subunit organization	39	0.2	3.00E-04	7.30E-03
negative regulation of sister chromatid segregation	5	0	3.10E-04	7.40E-03
system development	58	0.3	3.40E-04	8.10E-03
negative regulation of chromosome segregation	5	0	3.40E-04	8.10E-03
developmental process	71	0.3	3.40E-04	8.10E-03
animal organ development	46	0.2	3.50E-04	8.30E-03
establishment of chromosome localization	6	0	3.50E-04	8.30E-03

microtubule-based process	16	0.1	3.70E-04	8.60E-03
chromatin silencing at rDNA	5	0	3.70E-04	8.60E-03
central nervous system development	20	0.1	3.80E-04	8.60E-03
chromosome localization	6	0	3.80E-04	8.60E-03
mitotic spindle organization	5	0	4.10E-04	9.30E-03
cell development	33	0.1	4.10E-04	9.30E-03
regulation of intracellular signal transduction	30	0.1	4.30E-04	9.50E-03
single-organism developmental process	69	0.3	4.70E-04	1.00E-02
ear morphogenesis	7	0	5.20E-04	1.10E-02
multicellular organism development	63	0.3	5.40E-04	1.20E-02
regulation of gene expression, epigenetic	10	0	5.50E-04	1.20E-02
positive regulation of developmental process	22	0.1	5.70E-04	1.20E-02
regulation of signal transduction	41	0.2	5.80E-04	1.20E-02
negative regulation of mitotic nuclear division	5	0	6.00E-04	1.30E-02
head development	17	0.1	6.20E-04	1.30E-02
regulation of muscle tissue development	7	0	6.50E-04	1.40E-02
positive regulation of gene expression, epigenetic	6	0	6.60E-04	1.40E-02
positive regulation of macromolecule metabolic process	42	0.2	7.40E-04	1.50E-02
positive regulation of metabolic process	44	0.2	7.80E-04	1.60E-02
positive regulation of mitotic cell cycle	7	0	8.10E-04	1.60E-02
protein complex assembly	26	0.1	8.20E-04	1.70E-02
protein complex biogenesis	26	0.1	8.30E-04	1.70E-02
anatomical structure development	68	0.3	8.30E-04	1.70E-02
metaphase plate congression	5	0	8.30E-04	1.70E-02
movement of cell or subcellular component	30	0.1	9.00E-04	1.80E-02
macromolecular complex assembly	29	0.1	9.20E-04	1.80E-02
neuron migration	7	0	9.50E-04	1.90E-02
sister chromatid cohesion	7	0	9.50E-04	1.90E-02
regulation of protein binding	8	0	1.00E-03	2.00E-02
wound healing	14	0.1	1.00E-03	2.00E-02
brain development	16	0.1	1.10E-03	2.00E-02
regulation of biological process	115	0.5	1.10E-03	2.00E-02
regulation of organelle organization	22	0.1	1.20E-03	2.20E-02
connective tissue development	9	0	1.20E-03	2.20E-02
organelle localization	13	0.1	1.30E-03	2.50E-02
regulation of canonical Wnt signaling pathway	9	0	1.30E-03	2.50E-02
regulation of binding	10	0	1.40E-03	2.60E-02
developmental cell growth	8	0	1.40E-03	2.60E-02
inner ear morphogenesis	6	0	1.50E-03	2.70E-02
regulation of cellular process	111	0.5	1.50E-03	2.60E-02
regulation of G1/S transition of mitotic cell cycle	7	0	1.60E-03	2.80E-02
spindle assembly involved in meiosis	3	0	1.60E-03	2.80E-02
negative regulation of G1/S transition of mitotic cell cycle	6	0	1.60E-03	2.90E-02
regulation of transcription involved in G1/S transition of mitotic cell cycle	4	0	1.70E-03	3.00E-02
cell growth	12	0.1	1.70E-03	3.00E-02
positive regulation of cell cycle process	9	0	1.70E-03	3.10E-02
cell cycle G2/M phase transition	8	0	1.80E-03	3.20E-02
gene silencing	9	0	1.80E-03	3.20E-02
regulation of growth	15	0.1	1.90E-03	3.30E-02
organelle assembly	15	0.1	1.90E-03	3.30E-02
negative regulation of cell cycle G1/S phase transition	6	0	1.90E-03	3.30E-02
positive regulation of protein catabolic process	9	0	2.00E-03	3.40E-02
regulation of gene silencing	5	0	2.00E-03	3.50E-02
ear development	8	0	2.20E-03	3.70E-02
regulation of cell communication	42	0.2	2.20E-03	3.70E-02
morphogenesis of an epithelium	13	0.1	2.20E-03	3.70E-02

regulation of anatomical structure morphogenesis	20	0.1	2.20E-03	3.70E-02
regulation of cell cycle G1/S phase transition	7	0	2.40E-03	3.90E-02
axon extension	6	0	2.50E-03	4.00E-02
response to retinoic acid	6	0	2.50E-03	4.00E-02
negative regulation of chromosome organization	6	0	2.80E-03	4.50E-02
smooth muscle cell proliferation	6	0	2.80E-03	4.50E-02
regulation of signaling	42	0.2	3.10E-03	4.90E-02

S. Table 4. Enrichment analysis of upregulated expression of genes in patients in fibroblast cells

PDB code	Gene Symbol of the histone binding partner (except for nucleosome)	Histone state (modified or not, or with a mutated residue)
3AV2	FULL NUCLEOSOME	H3.3
3JVK	Brd4	H3.3-K(ac)14
3MUK	Brd4	H3.3-K(prop)23
4GNF	NSD3	UNMODIFIED
4GUS	KDM1B	K4 replaced by a Met, mimic H3K4me2
4N4I	Zmynd11	H3.3K36me3
4QQ4	MORC3	H3.3K4me3
4TMP	MLLT3	H3.3K9ac
5JLB	SETD2	H3.3 mutant K36I

S. Table 5. Table of PDB files utilized for structural location computation of the variants