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Supplemental Data

De Novo Loss-of-Function Mutations in *SETD5*, Encoding a Methyltransferase in a 3p25 Microdeletion Syndrome Critical Region, Cause Intellectual Disability

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Table S1: List of the 565 Genes that were Selected for Targeted Next Generation Sequencing

Gene IDs

ABCD1
ACBD6
ACE2
ACIN1
ACOT9
ACSL4
ACTL6A
ACTL6B
ACY1
ADCK3
ADK
ADRA2B
ADSL
AFF2
AGA
AGTR2
AIMP1
AKAP17A
AKAP4
ALDH18A1
ALDH4A1
ALDH5A1
ALG1
ALG12
ALG13
ALG3
ALG6
ALG8
ANK3
AP1S2
AP4B1
AP4E1
AP4M1
AP4S1
ARFGEF2
ARG1
ARHGAP36
ARHGAP6
ARHGEF4
ARHGEF6
ARHGEF9
ARID1A

ARID1B
ARID2
ARIH1
ARL14EP
ARSF
ARX
ASB12
ASCC3
ASCL1
ASH1L
ASMT
ASMTL
ASXL1
ATM
ATP2B3
ATP7A
ATRX
ATXN3L
AUH
AVPR2
AWAT2
BCOR
BCORL1
BDP1
BMP15
BRAF
BRWD3
BTK
C12orf57
CA8
CACNA1F
CACNA1G
CAMK2A
CAMK2G
CAP1
CAPN10
CASK
CASP2
CC2D1A
CC2D2A
CCDC22
CCDC23
CCNA2
CCNB3
CD99
CDH15

CDK16
CDK8
CDKL5
CEP41
CFP
CHD2
CHD7
CHL1
CLCN4
CLCN5
CLIC2
CMC4
CNKSR1
CNKSR2
CNTNAP2
COL4A3BP
COL4A6
COQ5
COX10
CPXCR1
CREBBP
CRLF2
CSF2RA
CSTF2
CTNNB1
CTPS2
CTSD
CTTNBP2
CUL4B
CUX2
CXORF22
CXORF58
CYP7B1
DCHS2
DCX
DDOST
DDX26B
DDX3X
DDX53
DEAF1
DGKH
DHCR7
DHRSX
DHX30
DIAPH2
DKC1

DLG1
DLG2
DLG3
DLG4
DMD
DNMT3B
DOCK11
DPF1
DPF2
DPF3
DYNC1H1
DYRK1A
EEF1A2
EEF1B2
EHMT1
EIF2C1
EIF2S3
ELK1
ELP2
ENOX2
ENTHD2
ENTPD1
EP300
EPPK1
ERCC6
ERLIN2
ESX1
EXOSC3
FAAH2
FAM120C
FAM47B
FAM58A
FASN
FGD1
FKBPL
FKRP
FKTN
FLNA
FMR1
FOXG1
FOXP1
FRMPD4
FRY
FTL
FTSJ1
GAB3

GABRQ
GAD1
GATAD2B
GCDH
GCH1
GDI1
GJC2
GK
GLB1
GLRA2
GM2A
GON4L
GPC3
GPR112
GPR56
GPRASP1
GRB14
GRIA1
GRIA2
GRIA3
GRIK2
GRIN2A
GRIN2B
GSPT2
GTPBP8
HAUS7
HCCS
HCFC1
HDAC4
HDAC8
HDHD1
HEXA
HEXB
HGSNAT
HIST1H4B
HIST3H3
HIVEP2
HPRT1
HRAS
HS6ST2
HSD17B10
HSPD1
HUWE1
IDS
IDUA
IFNAR2

IGSF1
IKBKG
IL1RAPL1
IL3RA
INPP4A
INPP5E
IQSEC2
ITGA4
ITIH6
KANK1
KANSL1
KAT6B
KCNC3
KCND1
KCNH1
KCNK12
KCNQ3
KDM1A
KDM5A
KDM5C
KDM6B
KIAA2022
KIF1A
KIF26B
KIF4A
KIF5C
KIF7
KIRREL3
KLHL15
KLHL21
KLHL34
KLHL4
KMT2D
KRAS
L1CAM
LAMA1
LAMP2
LARP7
LAS1L
LHFPL3
LIMK1
LINS
LRP1
LRP2
LRRK1
MAGEA11

MAGEB1
MAGEB10
MAGEB2
MAGEC1
MAGEC3
MAGED1
MAGEE2
MAGIX
MAGT1
MAN1B1
MAOA
MAOB
MAP2K1
MAP2K2
MAP3K15
MAP7D3
MBD5
MBNL3
MECP2
MED12
MED17
MED23
MEF2C
MGAT5B
MIB1
MID1
MLC1
MLH1
MLL3
MLYCD
MMAA
MMAB
MMADHC
MORC4
MSL3
MTF1
MTMR1
MTMR8
MXRA5
MYO1D
MYO1G
MYT1L
NA
NAA10
NDE1
NDP

NDST1
NDUFA1
NECAB2
NEU1
NF1
NFIX
NHS
NKAP
NLGN3
NLGN4X
NR1I3
NRK
NRXN1
NRXN2
NSD1
NSDHL
NSUN2
NTM
NXF4
NXF5
OCRL
ODF2L
OFD1
OGT
OPHN1
OR5M1
OTC
OXCT1
P2RY4
P2RY8
PABPC5
PAFAH1B1
PAH
PAK3
PARP1
PASD1
PAX6
PBRM1
PC
PCDH10
PCDH19
PCNT
PDHA1
PECR
PEPD
PGK1

PGRMC1
PHACTR1
PHF10
PHF6
PHF8
PHIP
PHKA1
PIGN
PIK3C3
PIN4
PJA1
PLA2G6
PLCXD1
PLP1
PLXNB3
PNKP
POLA1
POLR3A
POLR3B
PORCN
PPP2R5D
PPT1
PQBP1
PRDX4
PRICKLE3
PRMT10
PROX2
PRPS1
PRRG1
PRRG3
PRRT2
PRSS12
PSMA7
PSMD10
PTCHD1
PTEN
PTPN11
PTPN21
RAB39B
RAB3GAP1
RAB40AL
RABL6
RAF1
RAI1
RALGDS
RAPGEF1

RBM10
RENBP
RGAG1
RGN
RGS7
RLIM
RNASET2
RPGR
RPS6KA3
SATB2
SCAPER
SCN2A
SCN8A
SETBP1
SETD5
SETDB2
SGSH
SHANK1
SHANK2
SHANK3
SHOC2
SHOX
SHROOM2
SHROOM4
SLC12A6
SLC16A2
SLC25A22
SLC25A53
SLC25A6
SLC26A9
SLC2A1
SLC31A1
SLC6A1
SLC6A17
SLC6A8
SLC9A6
SMARCA2
SMARCA4
SMARCB1
SMARCC1
SMARCC2
SMARCD1
SMARCD2
SMARCD3
SMARCE1
SMC1A

SMS
SNTG1
SOS1
SOX3
SOX5
SPG11
SPRED1
SPRY3
SPTAN1
SPTLC2
SREBF2
SRGAP3
SRPX2
ST3GAL3
STAB2
STAG1
STARD8
STXBP1
SYN1
SYNCRIP
SYNE1
SYNGAP1
SYP
SYT1
SYTL4
SYTL5
TAF1
TAF2
TAF7L
TANC2
TAT
TBC1D24
TBC1D8B
TCEAL3
TCF4
TCP10L2
TENM1
THAP1
THOC2
ThumpD1
TIMM8A
TKTL1
TLR8
TM4SF2
TMEM132E
TMEM135

TMLHE
TNKS2
TNPO2
TRAPPC9
TREX2
TRIO
TRMT1
TSC1
TSC2
TSC22D3
TSEN2
TSEN34
TSEN54
TSPAN7
TTI2
TUBA1A
TUBA8
TUBAL3
TUBB2B
TUSC3
UBE2A
UBE3A
UBR1
UBR7
UBTF
UPF3B
USP27X
USP9X
UTP14A
VAMP7
VLDLR
VPS13B
VRK1
WAC
WDR11
WDR13
WDR45L
WDR62
WNK3
WWC3
XIAP
XKRX
YY1
ZBTB40
ZC3H14
ZCCHC12

ZCCHC8
ZDHHC15
ZDHHC9
ZEB2
ZFHX4
ZFX
ZFYVE26
ZMYM3
ZMYM6
ZMYND12
ZNF238
ZNF41
ZNF425
ZNF526
ZNF674
ZNF711
ZNF81

Table S2: Rationale for Prioritisation of Genes for Further Investigation

Top ranked genes according to number of rare variants in the ID cohort
(frequency <1% 1000 genomes, UK10K twins cohort, NHLBI GO Exome Sequencing Project Exome Variant Server (NHLBI EVS),
internal cohort 2172 individuals where whole exomes were sequenced at the same laboratory (UK10K) and the UK10K rare replication cohort itself (including all phenotypes))

LoF=Loss of function

ID gene	Number observed LoF variants	Frequency in ID cohort (%)
DCHS2	22	2.2
SYNE1	13	1.3
VPS13B	10	1.0
MIB1	9	0.9
NF1	9	0.9
ATM	8	0.8
PAH	7	0.7
PCDH10	7	0.7
SETD5	7	0.7
ASCC3	6	0.6
ATRX	6	0.6
UTP14A	6	0.6
HEXA	6	0.6
CC2D2A	6	0.6
STAB2	6	0.6

There are 15 genes in the ranking 1-10 as six genes were =10th with six observed LoF variants

The table from above was annotated with information as to how many of the variants are independent or if the same variants have been seen in multiple individuals
The criterion for independence was selected as it is unlikely that recurrent LoF variants in a gene will cause ID within the cohort

ID gene	Number observed LoF variants	Frequency in ID cohort (%)	How many are independent LoFs?	Number Independent LoFs
DCHS2	22	2.2	6 variants seen once; 1 variant seen 2 times; 1 seen 6 times; 1 seen 8 times	9
SYNE1	13	1.3	3 variants seen once; 1 variant seen 2 times; 1 variant seen 8 times	5
VPS13B	10	1.0	5 variants seen once; 1 variant seen 2 times; 1 variant seen 3 times	7
MIB1	9	0.9	5 variants seen once; 2 variants seen 2 times	7
NF1	9	0.9	1 variant seen once; 1 variant seen 2 times; 1 variant seen 6 times	3
ATM	8	0.8	6 variants seen once; 1 variant seen 2 times	7
PAH	7	0.7	4 variants seen once, 1 variant seen 3 times	5
PCDH10	7	0.7	1 variant seen 7 times	1
SETD5	7	0.7	7 variants seen once	7
ASCC3	6	0.6	6 variants seen once	6
ATRX	6	0.6	3 variants seen once; 1 variant seen 3 times	4
UTP14A	6	0.6	1 variant seen 6 times	1
HEXA	6	0.6	2 variants seen once; 2 variants seen 2 times	4
CC2D2A	6	0.6	6 variants seen once	6
STAB2	6	0.6	6 variants seen once	6

Sorted according to "Number Independent LoFs" column; Further information was added about the mode of inheritance, if it is a known or candidate gene, frequency of LoF variants in the NHLBI Exome sequencing Project
and the reason why the corresponding gene is excluded from further investigation

ID gene	Number Independent LoFs	Mode of inheritance	Known or candidate gene	Frequency NHLBI EVS LoF	Reason exclusion further analysis
DCHS2	9	Unknown	Candidate	13	Difficult to make judgement about possible pathogenicity of LoF variants in this gene as many were observed a few times; in addition 13 LoFs in NHLBI EVS
SETD5	7	Unknown	Candidate	1	
ATM	7	Recessive	Known	8	Known gene; recessive inheritance
VPS13B	7	Recessive	Known	17	Known gene
MIB1	7	Unknown	Candidate	13	Difficult to make judgement about possible pathogenicity of LoF variants in this gene as there are 12 LoF variants observed in NHLBI EVS
ASCC3	6	Recessive	Known	7	Known gene; recessive inheritance
CC2D2A	6	Recessive or Autosomal Dominant	Known	8	Known gene
STAB2	6	Unknown	Candidate	12	Difficult to make judgement about possible pathogenicity of LoF variants in this gene as there are 12 LoF variants observed in NHLBI EVS
PAH	5	Recessive	Known	4	Known gene
SYNE1	5	Recessive	Known	17	Known gene
ATRX	4	Hemizygous	Known	0	Known gene
HEXA	4	Recessive	Known	4	Known gene
NF1	3	Autosomal Dominant	Known	3	Known gene
PCDH10	1	Unknown	Candidate	1	No independent variants in this gene
UTP14A	1	Unknown	Candidate	0	No independent variants in this gene

SETD5 was selected for further investigation based on:
One of the genes with high number of independent LoFs
Candidate gene, not previously implicated in ID
Only one LoF observed in the publicly available data from NHLBI EVS

Table S3: Clinical Features of the Individuals with *SETD5* Mutations

FAMILY	1	2	3	4	5	6	7
birth weight (kg)	2.47	2.69	2.99	3.66	2.41	2.95	small
gestation (weeks)	34	38	term	term	35+5	term	term
Recent height (percentile)		50-75th	2nd		25-50th		
Recent weight (percentile)			9th		25-50th		
Recent Head Circumference (percentile)	25th	75-98th	50-75th	10-25th	75-91st	75th	10th
SPINE and SKELETON							
leg length discrepancy	y	y					
shortened 4th and 5th metacarpal		y					
hypoplasia of left calf		y					
scoliosis or kyphosis	y	y					
lordosis			y			y	
sacral dimple		y			y		
stiff legged gait					y	y	
bilateral 5th finger clinodactyly			y				
brachdactyly			y				
post axial polydactyly; 2 hands, 1 foot				y			
EARS							
large ears	y		y				
fleshy ear lobes		y			y		
long, narrow, low set ears			y				y
preauricular pit	y						
EYEBROWS							
full eyebrows		y					
synophrys	y		y				y
straight eyebrows	y						
broad eyebrows							y
cysts in eyebrows					y		
HEAD SHAPE							
brachycephaly	y	y					y
prominent high forehead					y		
NOSE							
broad, thickened upturned nasal tip		y			y		
depressed nasal bridge		y			y	y	
anteverted nares		y			y		
prominent high nasal root			y	y	y		y
tubular nose	y			y	y	y	
prominent nares			y				
EYES							
left eye amblyopia		y					
long narrow fissures			y		y		
mild ptosis					y		
nystagmus and strabismus				y			
down slanting palpebral fissures							y
upslanting palpebral fissures	y		y	y	y	y	
MOUTH and LOWER FACE							
long, smooth philtrum	y	y	y	y	y		
small mouth				y			y
short philtrum							y
micrognathia	y			y			y
thin upper lip	y	y	y		y		y
high palate	y						y

FEEDING AND SWALLOWING							
feeding difficuties	y	y					
crowded teeth		y				y	y
dribbling					y	y	y
difficulty chewing, oromotor dyspraxia					y	y	
swallowing difficulties		y				y	

BEHAVIOUR and DEVELOPMENT							
developmental delay	y	y	y	y	y	y	y
walking (age)	y (2yrs)	y (3yrs)	y (18mths)		y (2yrs)	y (3yrs 2mths)	y (20mths)
speech (age first words)	y (4yrs)	y (4 yrs)	y (12mths)	y (late)	y (18 mths)	y (2 years)	
expressive language delay					y	y	y
stammer	y		y	y			
exaggerated startle response						y	y
involutary movements			y			y	y (until 10yrs)
hand flapping and ritualised behaviour	y	y			y		
autistic	y					y	
obsessive compulsive disorder	y					y	y

CONGENITAL HEART DISEASE							
mitral valve prolapse		y					
VSD, PDA	y						

ABDOMINAL ORGAN DEVELOPMENT							
paraumbilical hernia					y		
inguinal hernia		y					y
undescended testes		y			y		
hypospadias	y		y				
nocturnal enuresis							y

OTHER							
fetal finger pads		y					
spiky hair		y					
saggy skin					y		
low hairline			y			y	y
severe constipation			y			y	