The American Journal of Human Genetics, Volume *89*

Supplemental Data

Exome Sequencing Identifies *CCDC8* Mutations in 3-M Syndrome, Suggesting that CCDC8 Contributes in a Pathway with CUL7 and OBSL1 to Control Human Growth

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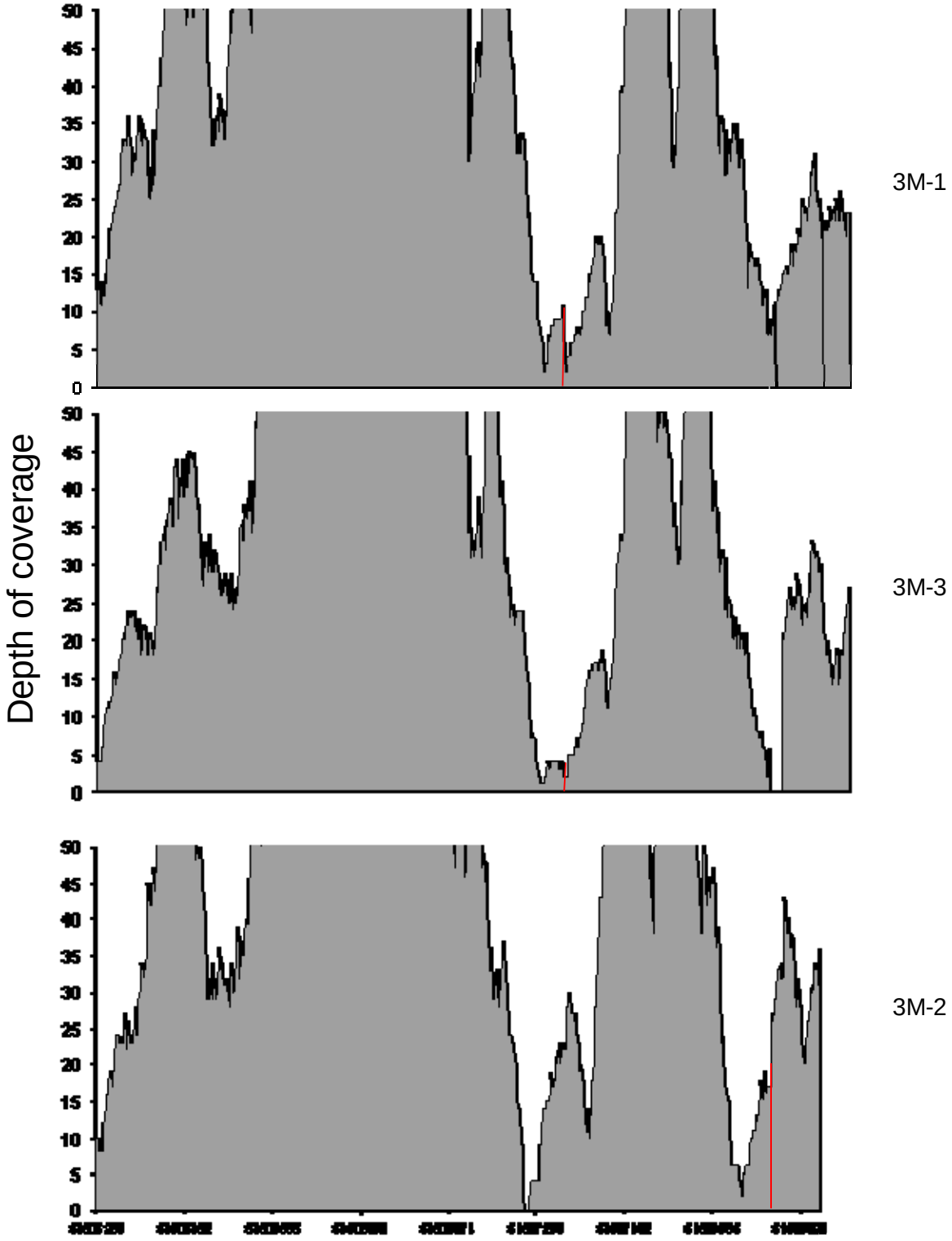

Figure S1. Exome Sequencing Coverage for Each 3-M Syndrome Individual

The red line marks the location of the mutation identified in each person. Note the low coverage seen in 3M-3 for the region surrounding c.612insG; this is due to high GC content.

Table S1. Previously Unidentified Sequence Variants in the Homozygous 19q13.2-q13.32 Region Found by Exome Sequencing of 3-M-1, -2, and -3

Variant	Location	Gene	Consequence	Position in cDNA	Position in protein	Amino acid change	RefAllele	Incidence
chr19:45594134_C/T	chr19:45594134	ENSG00000105227;PRX	SYNONYMOUS_CODING	c.1965	p.655	P	C	3M-1
chr19:45594209_C/T	chr19:45594209	ENSG00000105227;PRX	SYNONYMOUS_CODING	c.1890	p.630	K	C	3M-1
chr19:45594383_C/T	chr19:45594383	ENSG00000105227;PRX	SYNONYMOUS_CODING	c.1716	p.572	V	C	3M-1
chr19:46825142_T/C	chr19:46825142	ENSG00000105352;CEACAM4	SYNONYMOUS_CODING	c.30	p.10	G	T	3M-3
chr19:47487271_G/T	chr19:47487271	ENSG00000079432;CIC	NON_SYNONYMOUS_CODING	c.2511	p.837	Q/H	G	3M-2 and 3M-3
chr19:47934999_C/T	chr19:47934999	ENSG00000221826;PSG3	SYNONYMOUS_CODING	c.147	p.49	K	C	3M-1
chr19:48683042_G/A	chr19:48683042	ENSG00000176531;PHLDB3	NON_SYNONYMOUS_CODING	c.1223	p.409	P/L	G	3M-2
chr19:48929365_C/T	chr19:48929365	ENSG00000105771;C19orf61	SYNONYMOUS_CODING	c.1290	p.430	L	C	3M-1
chr19:49043957_G/A	chr19:49043957	ENSG00000159882;ZNF283	NON_SYNONYMOUS_CODING	c.1364	p.455	G/D	G	3M-3
chr19:49281840_CTC/-	chr19:49281840-49281842	ENSG00000186026;ZNF284	NON_SYNONYMOUS_CODING	c.527_529	123-124	FS/F	CTC	3M-1 and 2
chr19:49372654_G/A	chr19:49372654	ENSG00000167380;ZNF226	NON_SYNONYMOUS_CODING	c.1399	p.467	G/R	G	3M-1
chr19:49583144_C/A	chr19:49583144	ENSG00000184280;ZNF285	NON_SYNONYMOUS_CODING	c.1103	p.368	G/V	C	3M-1
chr19:49583168_C/G	chr19:49583168	ENSG00000184280;ZNF285	NON_SYNONYMOUS_CODING	c.1079	p.360	C/S	C	3M-1
chr19:50593157_C/T	chr19:50593157	ENSG00000104881;PPP1R13L	SYNONYMOUS_CODING	c.144	p.48	S	C	3M-3
chr19:50893966_C/A	chr19:50893966	ENSG00000011478;QPCTL	NON_SYNONYMOUS_CODING	c.854	p.285	T/K	C	3M-2
chr19:51005869_C/T	chr19:51005869	ENSG00000104941;RSPH6A	SYNONYMOUS_CODING	c.720	p.240	L	C	3M-2

Table S2. Haplotype Analysis of *CCDC8* (located at 19:51605469-51608681) Genomic Region with Identical Genotypes in 3M-1 and -3

SNP ID	db SNP ID	Chromosome	Physical Position	3M-1	3M-2	3M-3
SNP_A-8649112	rs4802307	19	51,541,646	AA	AA	AA
SNP_A-1856719	rs917946	19	51,551,898	BB	BB	NoCall
SNP_A-8539011	rs2239380	19	51,562,142	NoCall	NoCall	BB
SNP_A-8466857	rs6509265	19	51,563,993	BB	BB	BB
SNP_A-2222449	rs11671133	19	51,566,474	NoCall	BB	BB
SNP_A-1810596	rs1024782	19	51,579,407	AA	AA	NoCall
SNP_A-8598049	rs7359899	19	51,582,062	BB	BB	BB
SNP_A-8419960	rs12459321	19	51,598,837	NoCall	AA	BB
SNP_A-1809824	rs7246254	19	51,610,631	AA	AA	AA
SNP_A-1814614	rs453394	19	51,615,592	BB	AA	NoCall
SNP_A-8429472	rs1317877	19	51,618,224	BB	BB	BB
SNP_A-8592035	rs11083825	19	51,618,507	AA	AA	NoCall
SNP_A-8622580	rs10418662	19	51,621,865	AA	AA	NoCall
SNP_A-2033659	rs404997	19	51,621,987	BB	BB	BB
SNP_A-8436099	rs427250	19	51,623,902	AA	AA	NoCall
SNP_A-4199950	rs371657	19	51,629,571	AA	AA	AA
AFFX-SNP_11389240	rs371657	19	51,629,571	AA	AA	NoCall
SNP_A-8640758	rs11667187	19	51,640,083	AA	AA	AA
SNP_A-8520795	rs17728638	19	51,644,474	AA	AA	AA
SNP_A-2225336	rs8108405	19	51,646,246	BB	BB	BB
SNP_A-4195078	rs7254494	19	51,646,309	BB	BB	BB
SNP_A-1961664	rs4803953	19	51,650,847	AA	BB	AA
SNP_A-8334115	rs6509279	19	51,670,409	BB	AA	NoCall
SNP_A-8531024	rs16980543	19	51,694,755	BB	NoCall	BB
SNP_A-8712358	rs10403174	19	51,699,071	BB	NoCall	BB
SNP_A-8310429	rs7251461	19	51,700,261	AA	AA	AA
SNP_A-8373130	rs892106	19	51,706,775	BB	AA	BB
SNP_A-2089221	rs6509283	19	51,712,404	AA	BB	AA
SNP_A-8544931	rs745831	19	51,715,250	AA	BB	NoCall
SNP_A-8544508	rs10408465	19	51,717,495	AA	BB	NoCall

3M-2 has an alternative haplotype suggesting that c.612insG in 3M-1 and -3 is a founder mutation.

Table S3. SNPs Identified in CCDC8 in the ClinSeq Cohort of Controls

Gene	Position	Ref_allele	Var_allele	Ref_aa	Var_aa	aa_pos	SNP ID	CSc_homref	CSc_hetref	CSc_homnonref	CSc_hetnonref
CCDC8	51607022	C	T	G	R	296	rs11880658	398	3	0	0
CCDC8	51606995	C	G	E	Q	305	ss342568898	400	1	0	0
CCDC8	51606954	A	C	N	K	318	ss342568899	396	5	0	0
CCDC8	51606931	T	C	D	G	326	ss342568900	374	26	1	0
CCDC8	51606863	C	G	A	P	349	rs28498765	375	1	0	0
CCDC8	51606767	C	T	D	N	381	ss342568901	357	42	2	0
CCDC8	51606761	G	A	H	Y	383	rs34186470	271	118	12	0
CCDC8	51606387	C	G	K	N	507	rs2279517	357	41	2	0

Four novel missense SNPs and four previously identified SNPs in CCDC8 were present in a cohort of 401 controls. The variants identified in the 3-M individuals were not identified. These data together support the pathogenicity of CCDC8 mutations in 3-M syndrome.