Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

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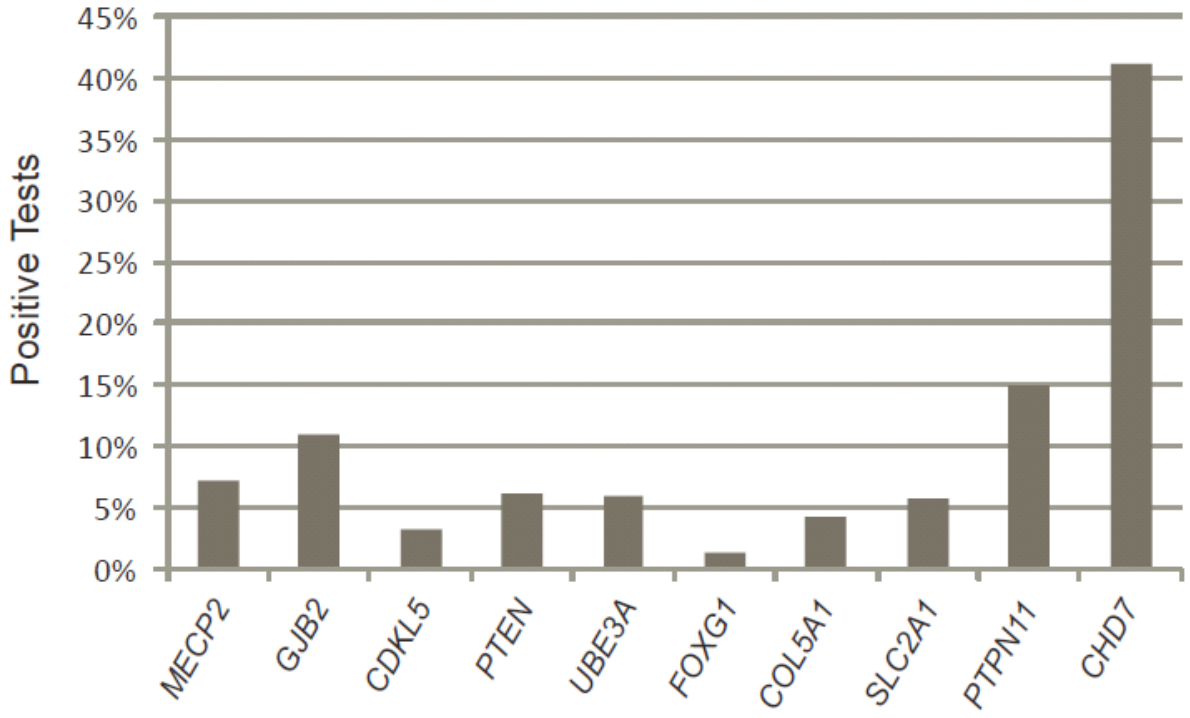

Figure S1. Comparison of Diagnostic Yield from Sanger Sequencing-Based Single Gene Testing

The figure demonstrates the percentage of positive test results for the ten most commonly ordered single gene tests performed using Sanger sequencing by the same academic diagnostic laboratory as that performing WES

Table S1. WES Sequencing Data of the 250 Samples

Illumina Platform	Unique Aligned (Mb)*	Total Pass filter (Mb)†	Avg % Align (PF) Read 1‡	Avg % Align (PF) Read 2§	Avg % Error rate Read 1‖	Avg % Error rate Read 2**	Unique-ness %††	Dupli-cate %§§	Total Reads Aligned %‖‖	Avg Coverage ***	Median Coverage †††	Reads hit target/ Buffer ‡‡‡	Bases 20+ coverage§§§	Bases 40+ coverage§§§
GAII	11,317	12,273	94.5	96.6	1.2	2.7	96.5	8.9	98.3	138.0	104.0	80.6	96.0	89.1
GAII	12,319	13,017	98.0	97.0	1.1	1.3	97.1	7.3	97.5	168.0	128.0	82.6	96.1	91.2
GAII	11,835	12,532	95.1	98.1	2.1	0.7	97.8	7.0	96.6	160.0	125.0	82.3	96.6	92.2
GAII	10,627	11,178	97.5	98.5	2.0	0.9	97.0	7.9	98.0	149.0	113.0	84.0	96.1	90.3
GAII	11,468	12,024	97.1	97.2	1.3	1.4	98.2	5.3	97.1	161.0	125.0	82.9	96.7	92.5
GAII	12,040	12,695	98.5	95.4	0.5	2.2	97.8	6.0	97.0	162.0	128.0	80.7	97.0	93.3
GAII	11,555	12,195	98.2	98.2	1.2	1.1	96.5	8.4	98.2	161.0	122.0	83.5	96.1	91.1
GAII	11,640	12,256	98.3	98.3	1.1	1.1	96.6	7.7	98.3	159.0	120.0	82.8	96.0	90.7
GAII	13,216	13,762	99.1	98.4	0.4	1.1	97.2	6.5	98.8	183.0	137.0	82.4	96.3	91.9
GAII	11,631	12,119	99.1	98.4	0.5	1.2	97.2	6.3	98.8	159.0	119.0	82.2	96.0	90.7
GAII	12,692	13,579	96.1	96.1	1.3	1.3	97.3	6.9	96.1	171.0	131.0	82.4	96.0	91.1
GAII	12,792	13,987	92.0	95.4	1.3	3.7	97.6	7.0	93.7	170.0	129.0	80.0	95.3	89.7
GAII	9,250	9,934	95.4	94.3	1.6	2.9	98.2	5.9	94.9	130.0	96.0	84.0	94.3	85.0
GAII	9,910	10,370	98.2	97.6	0.8	1.6	97.6	5.9	96.9	134.0	98.0	82.1	94.4	85.3
GAII	9,870	10,428	97.4	96.4	0.9	2.2	97.7	5.6	97.9	135.0	99.0	82.0	94.8	86.1
GAII	11,601	12,330	96.9	95.0	1.2	3.4	98.1	6.5	95.9	157.0	129.0	82.7	96.4	92.5
GAII	11,380	11,953	98.2	97.2	0.7	1.9	97.5	6.1	97.7	155.0	129.0	81.6	96.8	93.3
GAII	11,796	12,266	98.7	98.1	0.6	1.6	97.8	5.4	98.4	164.0	136.0	83.5	96.9	93.8
GAII	13,089	13,869	97.4	96.3	1.0	2.0	97.4	6.6	96.9	180.0	148.0	83.4	96.7	93.6
GAII	13,134	13,981	97.7	96.8	0.9	1.9	96.6	9.4	97.2	182.0	149.0	82.9	96.5	93.1
GAII	11,313	12,088	96.3	93.8	1.5	3.4	98.5	5.3	95.1	160.0	136.0	82.6	96.9	94.0
GAII	11,591	12,234	97.4	96.1	1.0	2.2	98.0	5.3	96.7	158.0	131.0	82.6	96.5	93.0
GAII	13,105	13,506	97.6	98.5	0.6	2.0	94.1	7.0	98.1	152.0	119.0	83.3	96.7	92.4
GAII	10,050	10,314	98.2	98.2	1.2	1.1	97.5	5.9	98.2	161.0	129.0	84.5	96.6	93.0
HiSeq	13,281	14,546	99.2	98.5	0.4	1.7	92.3	9.6	98.9	182.0	146.0	77.7	97.0	94.6
HiSeq	11,561	12,165	99.0	98.7	0.5	0.8	96.1	5.2	98.9	169.0	144.0	81.9	97.3	95.3
HiSeq	12,633	13,000	99.5	99.2	0.6	1.0	97.8	3.9	99.4	174.0	149.0	80.5	97.5	95.9
HiSeq	13,784	14,762	99.3	98.7	0.5	1.2	94.3	8.1	99.0	184.0	160.0	75.5	97.7	96.3
HiSeq	12,129	12,763	99.0	98.7	0.4	0.8	96.1	5.2	98.9	171.0	145.0	79.9	97.1	95.3
HiSeq	12,841	13,409	99.3	99.2	0.8	0.7	96.5	5.2	99.3	169.0	135.0	78.9	97.4	94.8
HiSeq	11,313	11,921	99.4	98.8	0.4	1.2	95.7	5.9	99.1	156.0	131.0	78.6	97.2	94.8
HiSeq	13,934	14,692	98.8	98.7	0.9	0.8	96.0	5.7	98.8	152.0	124.0	64.0	97.0	93.9
HiSeq	20,768	22,240	99.5	99.3	0.6	0.7	93.9	8.4	99.4	287.0	233.0	78.6	97.7	96.9
HiSeq	12,064	12,716	98.1	97.9	0.9	1.2	96.8	4.6	98.0	126.0	102.0	59.3	96.5	90.9
HiSeq	19,753	21,187	99.1	98.8	0.7	1.0	94.2	8.3	98.9	251.0	207.0	72.2	97.7	96.8
HiSeq	11,984	12,530	99.5	99.3	0.6	0.7	96.2	5.1	99.4	164.0	130.0	80.1	97.1	93.8
HiSeq	12,532	13,064	99.4	99.3	0.8	0.7	96.6	5.2	99.4	168.0	133.0	79.4	97.2	94.2

HiSeq	18,024	19,320	99.2	99.0	0.6	0.7	94.2	8.1	99.1	242.0	191.0	77.5	97.7	96.4
HiSeq	10,604	11,011	99.4	99.3	0.6	0.7	96.9	4.2	99.4	152.0	123.0	82.2	97.1	93.6
HiSeq	19,926	21,432	99.0	98.9	0.7	0.8	94.0	8.8	98.9	267.0	212.0	76.2	97.8	96.6
HiSeq	14,412	15,164	99.3	99.1	0.6	0.7	95.8	5.9	99.2	190.0	149.0	77.9	97.2	94.8
HiSeq	10,947	11,473	99.2	99.1	0.8	0.8	96.2	5.3	99.2	145.0	115.0	79.4	96.8	92.6
HiSeq	18,510	19,696	99.3	99.2	0.7	0.7	94.7	7.6	99.2	249.0	198.0	78.5	97.6	96.3
HiSeq	13,203	14,202	99.0	98.3	0.4	1.8	94.3	7.6	98.6	181.0	143.0	77.5	97.3	94.9
HiSeq	20,053	21,230	97.8	97.6	0.8	0.9	96.7	4.6	97.7	156.0	123.0	45.0	97.0	93.2
HiSeq	18,675	19,984	99.3	99.1	0.7	0.8	94.2	8.4	99.2	261.0	210.0	77.9	97.7	96.4
HiSeq	22,606	24,344	99.4	99.2	0.6	0.8	93.5	9.1	99.3	309.0	242.0	76.7	97.8	96.8
HiSeq	16,310	17,426	99.4	99.3	0.9	0.7	94.2	7.9	99.3	229.0	188.0	78.6	97.5	96.3
HiSeq	12,219	12,744	99.4	99.3	0.8	0.7	96.5	5.0	99.3	163.0	129.0	79.0	97.0	93.7
HiSeq	13,005	13,648	99.5	99.3	0.6	0.6	95.9	5.5	99.4	184.0	147.0	81.2	97.2	95.0
HiSeq	11,086	11,601	99.4	99.1	0.5	0.8	96.3	5.1	99.2	151.0	119.0	78.9	96.9	92.8
HiSeq	24,629	26,750	99.3	98.3	0.5	2.1	93.2	9.3	98.8	333.0	263.0	75.7	97.8	96.9
HiSeq	11,116	11,561	99.4	99.1	0.5	0.8	96.9	4.3	99.2	153.0	129.0	79.6	97.4	95.1
HiSeq	11,892	12,500	99.3	99.1	0.6	0.7	95.9	5.5	99.2	154.0	121.0	75.7	96.7	92.9
HiSeq	12,710	13,470	99.0	98.2	0.6	1.9	95.7	7.2	98.6	174.0	135.0	77.5	97.0	94.0
HiSeq	11,842	12,347	99.2	99.0	0.4	0.7	96.8	4.3	99.1	164.0	141.0	80.2	97.6	95.8
HiSeq	13,280	14,112	99.2	98.6	0.4	1.7	95.2	6.3	98.9	179.0	141.0	78.6	97.3	94.7
HiSeq	11,135	11,720	99.4	98.5	0.5	2.1	96.0	5.4	98.9	156.0	123.0	81.0	96.9	93.3
HiSeq	15,311	15,997	99.3	99.0	0.7	1.0	96.5	6.1	99.1	209.0	178.0	79.3	97.8	96.7
HiSeq	12,435	13,137	98.9	98.2	0.6	1.8	96.1	6.8	98.5	160.0	125.0	75.8	97.0	93.1
HiSeq	13,103	13,942	99.4	98.5	0.4	2.0	95.0	6.6	99.0	179.0	142.0	79.0	97.2	94.7
HiSeq	9,990	10,418	98.9	98.3	0.4	1.6	97.3	3.7	98.6	117.0	92.0	69.3	96.1	88.7
HiSeq	13,914	14,642	99.1	98.4	0.5	1.7	96.2	6.5	98.8	187.0	145.0	78.6	97.1	94.4
HiSeq	11,642	12,169	99.4	99.2	0.5	0.7	96.4	5.0	99.3	159.0	124.0	79.4	97.0	93.2
HiSeq	11,453	12,098	99.1	98.5	0.4	1.7	95.8	5.5	98.8	156.0	120.0	78.5	96.9	92.9
HiSeq	14,132	14,991	99.2	98.7	0.4	1.5	95.3	6.5	98.9	190.0	149.0	78.6	97.3	94.9
HiSeq	13,396	14,036	99.3	99.0	0.4	0.7	96.3	5.0	99.1	189.0	160.0	80.8	97.5	96.1
HiSeq	10,988	11,528	99.5	99.2	0.5	0.8	96.0	5.4	99.3	148.0	114.0	79.2	96.7	91.7
HiSeq	13,114	13,560	99.3	99.0	0.7	1.0	97.5	4.3	99.2	179.0	153.0	80.1	97.8	96.3
HiSeq	14,100	14,709	99.4	99.2	0.4	0.6	96.6	4.6	99.3	198.0	168.0	80.7	97.5	96.1
HiSeq	12,402	12,841	99.3	99.2	0.4	0.6	97.3	3.7	99.2	169.0	143.0	79.3	97.4	95.6
HiSeq	16,454	17,153	99.3	99.2	0.5	0.6	96.6	4.8	99.3	227.0	193.0	79.3	97.8	96.8
HiSeq	14,148	14,837	99.3	99.0	0.5	0.8	96.2	5.2	99.1	205.0	175.0	81.3	97.6	96.3
HiSeq	11,791	12,199	99.2	99.0	0.6	0.8	97.5	3.7	99.1	165.0	142.0	81.7	97.4	95.4
HiSeq	14,499	15,166	99.3	99.1	0.4	0.7	96.4	4.9	99.2	202.0	174.0	80.0	97.9	96.7
HiSeq	12,620	13,268	99.2	98.9	0.5	0.7	96.1	5.2	99.0	186.0	161.0	82.4	97.7	96.1
HiSeq	14,574	15,315	99.4	98.7	0.4	1.3	96.1	5.5	99.0	196.0	167.0	78.3	97.8	96.6

HiSeq	10,895	11,357	99.0	98.8	0.6	0.8	97.0	4.3	98.9	154.0	129.0	81.6	97.2	94.5
HiSeq	12,046	12,647	99.1	98.8	0.5	0.8	96.3	5.1	99.0	173.0	149.0	80.7	97.6	95.8
HiSeq	12,994	13,657	99.1	98.8	0.5	0.8	96.2	5.2	98.9	183.0	156.0	79.8	97.6	96.0
HiSeq	10,461	10,947	99.1	98.7	0.5	0.9	96.6	4.6	98.9	148.0	126.0	79.4	97.4	94.7
HiSeq	11,645	12,317	98.9	98.5	0.6	1.0	95.8	5.9	98.7	170.0	143.0	79.0	94.7	89.1
HiSeq	11,499	12,197	98.8	98.5	0.6	0.9	95.6	6.5	98.7	167.0	141.0	78.6	96.1	91.7
HiSeq	9,403	9,807	99.1	98.8	0.5	0.8	96.9	4.1	99.0	135.0	116.0	81.4	96.9	93.1
HiSeq	14,502	15,321	99.2	98.3	0.5	1.6	95.9	5.6	98.8	201.0	173.0	79.5	97.5	96.3
HiSeq	13,310	14,000	99.2	98.9	0.4	0.7	96.0	5.2	99.1	189.0	163.0	80.9	97.8	96.4
HiSeq	12,902	13,680	98.8	98.4	0.5	1.0	95.7	6.3	98.6	186.0	159.0	78.2	96.5	92.6
HiSeq	13,747	14,362	99.2	99.0	0.5	0.7	96.6	4.7	99.1	188.0	161.0	79.0	97.7	96.3
HiSeq	13,702	14,381	99.2	98.9	0.4	0.7	96.2	5.3	99.1	196.0	169.0	79.8	97.8	96.4
HiSeq	10,876	11,364	99.2	98.4	0.4	1.4	96.9	4.3	98.8	151.0	131.0	80.7	97.6	95.5
HiSeq	10,669	11,257	98.9	98.6	0.4	0.7	96.0	5.2	98.7	152.0	129.0	81.0	97.1	94.7
HiSeq	14,241	15,080	98.7	98.3	0.4	0.7	95.9	5.4	98.5	191.0	165.0	77.7	97.6	96.3
HiSeq	11,863	12,828	98.9	97.7	0.6	1.6	94.1	8.4	98.3	161.0	140.0	76.4	97.7	95.8
HiSeq	14,410	15,084	99.2	98.9	0.4	0.7	96.4	4.9	99.1	199.0	170.0	79.5	97.6	96.4
HiSeq	11,503	12,209	98.9	98.3	0.5	0.9	95.6	5.9	98.6	157.0	135.0	77.4	97.7	95.6
HiSeq	15,435	16,436	99.1	98.7	0.5	0.9	95.0	6.6	98.9	214.0	184.0	78.7	97.9	96.9
HiSeq	12,767	13,397	99.2	99.0	0.4	0.6	96.2	5.0	99.1	182.0	157.0	81.4	97.7	96.2
HiSeq	12,999	13,603	99.3	98.5	0.5	1.4	96.6	4.9	98.9	178.0	151.0	79.0	97.7	96.1
HiSeq	15,368	16,169	99.2	99.0	0.4	0.7	95.9	5.4	99.1	218.0	188.0	80.4	97.9	96.8
HiSeq	14,437	15,084	99.3	99.1	0.4	0.6	96.5	4.7	99.2	204.0	175.0	80.7	97.6	96.4
HiSeq	10,027	10,385	99.2	99.0	0.4	0.6	97.5	3.4	99.1	143.0	121.0	81.6	97.2	94.3
HiSeq	13,313	13,868	99.1	98.8	0.5	0.7	97.0	4.0	99.0	186.0	160.0	80.5	97.8	96.4
HiSeq	10,946	11,366	99.2	99.0	0.4	0.6	97.2	3.7	99.1	156.0	134.0	81.7	97.5	95.4
HiSeq	13,849	14,513	99.2	98.8	0.5	0.8	96.4	5.0	99.0	187.0	158.0	78.1	97.8	96.4
HiSeq	9,177	9,505	99.3	99.0	0.4	0.7	97.4	3.5	99.1	129.0	110.0	81.2	96.9	93.3
HiSeq	13,688	14,472	99.2	98.2	0.5	1.6	95.9	5.6	98.7	181.0	156.0	76.6	97.6	96.2
HiSeq	13,703	14,362	99.3	99.0	0.4	0.6	96.3	4.9	99.1	190.0	164.0	80.0	97.7	96.4
HiSeq	11,528	12,018	99.2	98.9	0.4	0.7	96.9	4.2	99.0	158.0	135.0	79.7	97.3	95.2
HiSeq	9,409	9,871	99.1	98.1	0.5	1.7	96.7	4.7	98.6	133.0	114.0	81.3	96.9	93.6
HiSeq	9,082	9,375	99.3	98.4	0.4	1.3	98.0	3.0	98.9	126.0	107.0	80.9	97.1	93.3
HiSeq	13,056	13,705	99.3	98.5	0.5	1.3	96.4	5.2	98.9	178.0	153.0	79.5	97.4	95.9
HiSeq	11,232	11,597	99.5	99.0	0.6	1.0	97.6	4.4	99.2	151.0	130.0	80.0	97.3	95.1
HiSeq	14,371	15,092	99.3	98.6	0.5	1.3	96.3	5.4	98.9	201.0	171.0	79.1	97.9	96.6
HiSeq	10,980	11,454	99.3	98.7	0.5	1.3	96.8	4.4	99.0	156.0	134.0	81.8	97.7	95.5
HiSeq	11,675	12,060	99.3	98.8	0.6	1.2	97.7	4.2	99.1	163.0	141.0	81.4	97.6	95.7
HiSeq	11,325	11,966	99.1	98.5	0.6	1.5	95.8	6.1	98.8	160.0	138.0	80.3	97.7	95.6
HiSeq	10,909	11,291	99.4	99.0	0.6	1.1	97.4	4.5	99.2	152.0	130.0	81.3	97.4	95.2
HiSeq	11,587	12,075	99.3	98.7	0.5	1.4	96.9	4.5	99.0	164.0	141.0	80.9	97.4	94.8
HiSeq	11,608	12,151	99.3	98.7	0.5	1.4	96.5	5.0	99.0	162.0	139.0	81.1	97.5	95.6
HiSeq	12,968	13,543	99.3	98.7	0.5	1.3	96.7	4.7	99.0	179.0	155.0	80.1	97.7	96.3
HiSeq	13,121	13,670	99.3	98.7	0.5	1.3	96.9	4.4	99.0	186.0	159.0	81.1	97.6	96.1
HiSeq	10,165	10,764	99.1	98.3	0.5	1.6	95.7	6.0	98.7	145.0	124.0	80.8	97.3	94.6
HiSeq	13,036	13,663	99.3	98.5	0.5	1.4	96.5	5.1	98.9	179.0	153.0	80.1	97.5	96.0

HiSeq	11,649	12,288	99.0	98.1	0.5	1.6	96.2	5.6	98.5	161.0	136.0	77.9	97.5	95.2
HiSeq	13,405	14,026	99.3	98.6	0.5	1.3	96.6	4.9	99.0	184.0	157.0	79.6	97.7	96.2
HiSeq	14,917	15,833	99.4	99.0	0.5	0.8	95.0	6.5	99.2	205.0	172.0	77.6	97.6	96.4
HiSeq	12,764	13,385	99.2	98.4	0.5	1.5	96.5	5.0	98.8	176.0	148.0	79.0	97.8	95.9
HiSeq	13,600	14,225	99.3	98.7	0.5	1.3	96.6	4.8	99.0	188.0	160.0	79.3	97.7	96.2
HiSeq	12,666	13,165	99.3	98.7	0.5	1.2	97.2	4.2	99.0	175.0	149.0	79.6	97.6	95.9
HiSeq	14,458	15,286	99.4	99.1	0.5	0.8	95.3	6.1	99.2	201.0	170.0	78.8	97.8	96.6
HiSeq	12,836	13,432	99.3	99.0	0.5	0.8	96.4	4.8	99.2	181.0	151.0	79.5	97.6	95.8
HiSeq	11,893	12,397	99.4	99.0	0.5	0.8	96.7	4.4	99.2	160.0	135.0	78.7	97.6	95.6
HiSeq	13,830	14,484	99.3	99.0	0.5	0.8	96.3	5.0	99.1	189.0	159.0	78.8	97.7	96.3
HiSeq	12,908	13,537	99.2	98.8	0.5	0.8	96.3	4.9	99.0	179.0	151.0	79.8	97.6	96.0
HiSeq	14,305	15,024	99.2	99.0	0.5	0.8	96.1	5.3	99.1	192.0	162.0	78.3	97.8	96.5
HiSeq	10,909	11,309	99.2	98.9	0.5	0.7	97.4	3.5	99.1	155.0	130.0	80.7	97.3	94.8
HiSeq	13,878	14,743	99.2	98.8	0.5	0.9	95.1	6.6	99.0	197.0	168.0	78.8	97.8	96.4
HiSeq	18,348	20,027	97.7	96.5	0.7	2.6	94.3	8.7	97.1	266.0	230.0	78.8	98.0	97.1
HiSeq	12,015	12,583	99.1	98.8	0.5	0.8	96.5	4.7	99.0	160.0	135.0	78.1	97.6	95.6
HiSeq	12,024	12,680	99.2	98.9	0.5	0.8	95.8	5.6	99.0	159.0	135.0	77.8	97.7	95.7
HiSeq	14,522	15,107	99.4	99.0	0.6	1.1	96.9	5.6	99.2	197.0	168.0	79.8	97.6	96.3
HiSeq	13,620	14,394	99.2	98.8	0.5	0.8	95.6	5.9	99.0	184.0	156.0	78.2	97.8	96.4
HiSeq	13,319	13,981	99.1	98.8	0.5	0.8	96.3	5.1	99.0	177.0	150.0	77.9	97.8	96.2
HiSeq	13,724	14,522	99.2	98.7	0.5	0.9	95.5	6.1	98.9	190.0	163.0	78.3	97.9	96.5
HiSeq	12,693	13,450	99.3	98.8	0.5	0.9	95.3	6.4	99.0	173.0	148.0	77.2	97.8	96.2
HiSeq	12,871	13,460	99.3	99.0	0.5	0.9	96.4	4.9	99.2	181.0	153.0	79.7	97.5	95.9
HiSeq	12,332	12,785	99.5	99.2	0.4	0.9	97.1	3.9	99.3	172.0	147.0	80.7	97.5	95.8
HiSeq	13,988	14,699	99.3	99.0	0.5	0.9	96.0	5.4	99.1	189.0	159.0	78.1	97.6	96.2
HiSeq	18,590	19,673	99.5	99.1	0.4	1.0	95.2	6.6	99.3	255.0	217.0	77.8	97.9	97.1
HiSeq	12,659	13,190	99.5	99.2	0.4	1.0	96.6	4.7	99.3	175.0	148.0	79.8	97.6	95.9
HiSeq	14,857	16,236	99.2	98.5	0.6	1.4	92.6	12.2	98.9	198.0	172.0	73.0	97.8	96.5
HiSeq	12,362	12,986	99.6	99.2	0.4	1.1	95.8	5.6	99.4	171.0	144.0	79.8	97.4	95.7
HiSeq	14,215	15,075	99.5	99.1	0.4	1.2	95.0	6.7	99.3	193.0	163.0	77.7	97.6	96.3
HiSeq	12,671	13,188	99.6	99.2	0.4	0.9	96.7	4.6	99.4	170.0	145.0	78.6	97.8	96.1
HiSeq	16,370	17,135	99.5	99.2	0.4	0.9	96.2	5.2	99.3	228.0	197.0	79.8	97.9	96.9
HiSeq	13,382	13,915	99.5	99.2	0.4	0.9	96.8	4.4	99.4	186.0	159.0	80.5	97.7	96.3
HiSeq	13,434	13,930	99.5	99.2	0.6	1.0	97.1	5.1	99.3	183.0	157.0	80.2	97.7	96.2
HiSeq	16,090	17,037	99.6	99.2	0.4	1.0	95.0	6.5	99.4	217.0	188.0	78.7	98.0	97.0
HiSeq	15,903	16,807	99.5	99.1	0.4	1.0	95.3	6.2	99.3	218.0	186.0	79.3	97.7	96.6
HiSeq	17,439	18,305	99.3	99.0	0.4	1.0	96.1	5.5	99.2	246.0	213.0	80.1	98.0	97.1
HiSeq	17,609	18,460	99.2	98.6	0.6	1.2	96.4	6.7	98.9	235.0	203.0	76.9	97.9	96.9
HiSeq	12,694	13,393	97.7	96.2	0.6	3.5	97.8	4.6	96.9	172.0	149.0	79.2	97.6	95.9
HiSeq	14,040	14,555	99.4	99.1	0.6	1.0	97.2	5.0	99.2	190.0	165.0	79.7	97.8	96.5
HiSeq	15,551	16,307	98.7	97.5	0.6	2.9	97.2	5.1	98.1	217.0	186.0	81.0	97.5	96.4
HiSeq	11,455	12,139	97.7	96.2	0.6	3.4	97.3	5.3	97.0	158.0	136.0	80.8	97.4	95.3
HiSeq	11,470	12,000	98.7	97.8	0.6	2.1	97.3	4.2	98.3	162.0	139.0	81.6	97.4	95.4
HiSeq	15,296	16,163	99.1	98.7	0.5	0.9	95.7	5.9	98.9	194.0	166.0	76.2	97.9	96.6
HiSeq	14,066	14,848	98.5	97.6	0.6	2.0	96.6	5.5	98.0	196.0	168.0	79.6	97.5	96.1
HiSeq	18,859	20,195	98.5	97.2	0.6	3.0	95.5	7.8	97.8	258.0	221.0	78.0	98.0	97.1

HiSeq	15,283	16,035	98.9	98.2	0.6	1.8	96.7	5.2	98.5	206.0	179.0	79.4	97.9	96.8
HiSeq	13,854	14,758	97.7	96.1	0.6	3.4	96.9	6.1	96.9	183.0	157.0	78.3	97.6	96.1
HiSeq	12,957	13,489	99.4	99.1	0.4	0.9	96.8	4.4	99.3	183.0	156.0	81.4	97.4	95.9
HiSeq	11,985	12,523	98.6	97.4	0.6	3.0	97.7	4.4	98.0	164.0	141.0	80.1	97.3	95.3
HiSeq	10,968	11,479	98.5	97.5	0.6	2.3	97.5	3.9	98.0	155.0	132.0	81.5	97.3	94.9
HiSeq	13,741	14,464	99.3	99.0	0.5	0.9	95.8	5.4	99.1	194.0	165.0	80.2	97.7	96.3
HiSeq	16,215	16,979	99.1	98.6	0.5	1.3	96.6	6.1	98.9	225.0	192.0	80.0	97.7	96.6
HiSeq	10,488	10,819	99.2	98.7	0.5	1.3	98.0	3.7	98.9	146.0	125.0	81.6	97.4	94.9
HiSeq	9,535	9,946	99.0	98.2	0.5	1.8	97.2	4.3	98.6	131.0	112.0	81.4	97.0	93.8
HiSeq	13,458	14,044	99.5	99.2	0.4	0.8	96.5	4.7	99.3	188.0	161.0	80.6	97.4	96.0
HiSeq	10,586	10,944	99.1	98.7	0.5	1.3	97.8	3.8	98.9	146.0	125.0	81.7	97.3	94.9
HiSeq	11,911	12,388	99.5	99.2	0.4	0.8	96.8	4.2	99.3	170.0	146.0	81.5	97.3	95.5
HiSeq	12,108	12,563	99.0	98.5	0.5	1.3	97.6	4.1	98.8	164.0	142.0	79.0	97.4	95.5
HiSeq	11,976	12,409	99.1	98.6	0.5	1.3	97.6	4.3	98.9	164.0	141.0	81.1	97.6	95.8
HiSeq	13,119	13,760	99.4	99.2	0.4	0.8	96.0	5.1	99.3	186.0	159.0	80.4	97.4	95.9
HiSeq	11,237	11,678	99.5	99.1	0.4	0.9	96.9	4.1	99.3	154.0	133.0	80.1	97.3	95.1
HiSeq	11,124	11,595	99.0	98.5	0.5	1.4	97.2	4.7	98.7	153.0	130.0	80.4	97.3	95.0
HiSeq	14,413	14,953	99.3	99.1	0.8	0.9	97.2	4.7	99.2	199.0	171.0	79.7	97.8	96.6
HiSeq	14,270	14,850	99.3	99.0	0.5	1.0	96.9	4.2	99.1	198.0	168.0	79.5	97.6	96.2
HiSeq	14,800	15,543	99.4	99.1	0.4	0.9	96.0	5.3	99.2	201.0	171.0	78.5	97.5	96.3
HiSeq	12,912	13,568	99.5	99.2	0.4	0.9	95.8	5.3	99.3	175.0	149.0	79.1	97.7	96.1
HiSeq	13,771	14,300	99.4	99.1	0.4	1.0	97.0	4.1	99.3	187.0	160.0	79.5	97.7	96.4
HiSeq	17,826	18,921	98.9	98.6	0.5	0.8	95.4	6.3	98.8	248.0	214.0	78.9	97.9	97.0
HiSeq	15,764	16,416	99.4	99.1	0.4	1.0	96.7	4.4	99.3	213.0	183.0	78.8	97.7	96.7
HiSeq	15,663	16,325	99.4	99.1	0.4	1.0	96.7	4.6	99.3	216.0	186.0	79.3	97.8	96.7
HiSeq	16,832	17,418	99.4	99.1	0.7	0.9	97.4	4.6	99.3	230.0	196.0	79.2	97.8	96.9
HiSeq	16,337	17,108	99.1	98.8	0.7	1.1	96.5	5.9	98.9	225.0	194.0	78.0	97.8	96.7
HiSeq	16,493	17,582	99.4	99.0	0.4	1.0	94.6	7.1	99.2	231.0	198.0	78.2	97.9	96.9
HiSeq	15,712	16,518	99.2	98.9	0.7	1.0	96.1	6.9	99.0	221.0	187.0	79.8	97.7	96.6
HiSeq	11,555	12,124	99.0	98.5	0.5	1.0	96.5	4.9	98.8	154.0	131.0	78.5	97.4	95.1
HiSeq	14,228	14,989	99.3	98.9	0.5	0.9	95.8	5.8	99.1	196.0	167.0	79.0	97.6	96.2
HiSeq	14,246	14,903	99.2	98.9	0.5	0.9	96.5	4.8	99.0	196.0	166.0	79.3	97.7	96.4
HiSeq	13,816	14,455	99.1	98.7	0.7	1.1	96.7	6.1	98.9	185.0	158.0	78.2	97.7	96.3
HiSeq	11,936	12,720	99.4	99.1	0.5	0.8	94.6	6.9	99.2	162.0	137.0	78.2	97.3	95.5
HiSeq	15,778	16,995	98.5	97.8	0.6	1.2	94.6	7.8	98.2	211.0	180.0	74.4	97.7	96.5
HiSeq	13,886	14,582	99.2	98.9	0.5	0.8	96.2	5.1	99.0	190.0	162.0	79.7	97.7	96.4
HiSeq	15,560	16,334	99.0	98.7	0.5	0.8	96.4	4.9	98.9	197.0	170.0	75.4	97.8	96.7
HiSeq	18,038	19,142	99.0	98.6	0.5	0.9	95.4	6.3	98.8	240.0	204.0	77.6	97.9	97.0
HiSeq	16,323	17,353	98.9	98.5	0.5	1.0	95.3	6.5	98.7	211.0	179.0	76.1	98.0	96.8
HiSeq	14,498	15,267	98.9	98.4	0.5	1.0	96.3	5.5	98.7	185.0	158.0	76.2	97.9	96.4
HiSeq	14,161	14,971	99.0	98.5	0.6	1.1	95.8	6.0	98.8	199.0	169.0	79.6	97.6	96.3
HiSeq	16,234	17,049	98.8	98.5	0.6	0.9	96.5	4.7	98.7	208.0	179.0	72.1	97.7	96.5
HiSeq	15,395	16,082	99.3	99.0	0.5	0.9	96.5	4.7	99.2	215.0	184.0	80.3	97.7	96.7
HiSeq	13,632	14,286	99.2	98.8	0.6	1.0	96.4	5.0	99.0	188.0	160.0	79.3	97.6	96.2
HiSeq	11,760	12,224	99.2	99.0	0.5	0.9	97.1	3.9	99.1	166.0	142.0	80.7	97.4	95.4
HiSeq	14,105	14,779	99.1	98.8	0.5	0.9	96.5	4.7	98.9	186.0	160.0	76.2	97.7	96.4

HiSeq	13,421	14,066	99.2	98.8	0.6	1.0	96.4	5.0	99.0	188.0	159.0	80.2	97.5	96.0
HiSeq	12,417	12,981	99.1	98.6	0.6	1.1	96.8	4.5	98.8	174.0	149.0	79.6	97.6	95.8
HiSeq	13,981	14,721	99.3	99.0	0.5	0.8	95.8	5.6	99.1	193.0	163.0	79.4	97.8	96.4
HiSeq	12,543	13,114	99.3	99.0	0.6	0.8	96.5	4.6	99.1	172.0	146.0	79.7	97.7	96.0
HiSeq	14,138	14,833	99.3	99.1	0.5	0.9	96.1	5.3	99.2	199.0	171.0	81.1	97.8	96.6
HiSeq	12,946	13,416	99.4	99.0	0.5	1.0	97.3	3.8	99.2	179.0	154.0	80.8	97.6	96.1
HiSeq	16,093	17,171	99.3	99.0	0.6	0.8	94.5	6.9	99.2	227.0	195.0	78.9	97.9	97.0
HiSeq	13,643	14,246	99.3	99.1	0.5	0.8	96.5	4.7	99.2	191.0	164.0	80.3	97.7	96.4
HiSeq	15,818	16,736	99.4	99.0	0.4	0.9	95.3	6.3	99.2	220.0	187.0	79.2	97.8	96.7
HiSeq	15,770	16,611	99.4	99.1	0.5	0.9	95.7	5.7	99.2	216.0	184.0	78.9	97.9	96.9
HiSeq	11,667	12,272	99.3	99.0	0.6	0.9	95.9	5.2	99.1	160.0	137.0	80.1	97.5	95.6
HiSeq	14,546	15,276	99.2	98.8	0.5	1.0	96.2	5.4	99.0	209.0	180.0	81.1	97.8	96.6
HiSeq	13,940	14,617	99.2	98.8	0.4	1.0	96.3	4.8	99.0	189.0	162.0	77.7	97.6	96.3
HiSeq	13,015	13,689	99.2	98.9	0.5	0.9	96.0	5.2	99.0	178.0	150.0	79.1	97.5	95.8
HiSeq	13,904	14,570	99.4	99.0	0.4	0.8	96.2	5.0	99.2	196.0	169.0	79.9	97.6	96.4
HiSeq	17,417	18,382	99.3	98.9	0.4	1.0	95.6	6.2	99.1	247.0	213.0	79.6	98.0	97.1
HiSeq	12,774	13,310	99.3	99.0	0.4	0.8	96.8	4.3	99.1	186.0	160.0	82.3	97.6	96.1
HiSeq	13,286	13,973	99.2	98.9	0.4	0.8	96.0	5.7	99.1	191.0	165.0	80.6	97.6	96.2
HiSeq	13,862	14,477	99.5	99.2	0.4	0.8	96.4	4.8	99.3	194.0	167.0	80.7	97.7	96.5
HiSeq	10,352	10,953	98.3	97.8	0.5	1.0	96.4	5.0	98.1	144.0	122.0	80.3	97.4	94.6
HiSeq	16,155	17,028	99.4	99.1	0.4	0.8	95.6	5.8	99.2	227.0	196.0	80.1	98.0	97.1
HiSeq	12,824	13,629	98.5	98.2	0.5	0.7	95.7	6.1	98.3	183.0	157.0	79.9	97.5	96.0
HiSeq	17,385	18,118	99.4	99.1	0.4	0.9	96.7	4.8	99.3	246.0	212.0	80.2	98.0	97.1
HiSeq	13,866	14,445	99.6	99.4	0.4	0.7	96.5	4.5	99.5	199.0	172.0	82.1	98.0	96.8
HiSeq	9,585	10,008	98.7	98.4	0.4	0.8	97.2	4.0	98.5	137.0	118.0	80.8	97.2	94.2

* Unique Aligned (Mbp): the total number of base-pairs in reads that align best to a single location in the reference genome

†Total Pass Filter (Mbp): the total number of base-pairs in reads that pass the Illumina quality filters

‡Avg % Align (PF) Read 1: the average percentage of pass filter base-pairs in Read 1 that align best to a single location in the reference genome

§ Avg % Align (PF) Read 2: the average percentage of pass filter base-pairs in Read 2 that align best to a single location in the reference genome

‖ Avg % Error rate Read 1: the calculated error rate of bases on Read 1, as determined by aligning to reference genome

**Avg % Error rate Read 2: the calculated error rate of bases on Read 2, as determined by aligning to reference genome

†† percentafe of unique reads

§§ duplicate %: fraction of reads that are identified as duplicate reads – reads whose alignment location is identical to other reads from the same library

‖‖Total Reads Aligned: the number of reads that align to the reference genome

***Average Coverage: the total number of uniquely aligned bases to the reference genome divided by the size of the reference genome

†††Median Coverage: the median number of reads of uniquely aligned bases

‡‡‡Reads hit target/buffer: the number of reads whose alignments overlap either a region targeted by the capture reagent, or the 100bp buffer (or both)

§§§Bases 20+ or 40+ Coverage: the fraction of bases targeted by the capture reagent that are covered by 20 or 40 times or more uniquely aligned reads.

Table S2. Prior Testing Information On Positive WES Cases from Local Referrals

Gene	Associated Phenotype	Inheritance	Chromosome	CMA	Singe-Gene	Mitochondrial	Gene Panel	Biopsy	Imaging	Biochemical Analyses
COL3A1	Ehlers-Danlos syndrome type 4	AD	N/A	Yes	FRDA	Yes	N/A	N/A	Yes	N/A
SCN8A	Epileptic encephalopathy, early infantile, 13	AD	N/A	Yes	MECP2, EMD	Yes	N/A	Yes	Yes	Yes
SRCAP	Floating-Harbor syndrome	AD	Yes	Yes	N/A	N/A	N/A	Yes	Yes	N/A
ARID1A	Mental retardation, Coffin Siris	AD	N/A	Yes	PTPN11 SOS1 KRAS	N/A	N/A	Yes	Yes	Yes
KRAS	Noonan syndrome; CFC	AD	N/A	Yes	FGFR2 FGFR3 FLNA	N/A	N/A	Yes	Yes	N/A
CBL	Noonan syndrome-like disorder	AD	Yes	Yes	Nemaline Myotubular myopathy	N/A	Noonan	N/A	Yes	Yes
SHANK3	Phelan-McDermid syndrome	AD	N/A	Yes	Prader-Willi FMR1	N/A	N/A	N/A	Yes	Yes
SETBP1 CLCN1	1) Schinzel-Giedion midface retraction syndrome; 2) Myotonia congenita	AD, AR	N/A	Yes	CYP27A1 FRDA GALC PLP1	N/A	N/A	N/A	Yes	Yes
WDR19	Asphyxiating thoracic dystrophy 5;	AR	N/A	Yes	DYNC2H1 IFT80	N/A	N/A	N/A	Yes	N/A

	Cranioectodermal dysplasia 4; Nephronophthisis 13									
FBLN5	Cutis laxa autosomal recessive type 1	AR	N/A	Yes	HRAS	N/A	N/A	N/A	N/A	N/A
ATRX	Alpha-thalassemia/mental retardation syndrome	X-linked	N/A	Yes	ARSA CDKL5 MECP2 PLP1 POLG1 UBE3A	Yes	N/A	N/A	N/A	Yes
ATRX	Alpha-thalassemia/mental retardation syndrome	X-linked	N/A	Yes	N/A	N/A	N/A	N/A	Yes	N/A
OFD1	Joubert syndrome 10	X-linked	Yes	Yes	AHI1 CEP290 NPHP TMEM67	N/A	N/A	N/A	Yes	Yes
CASK	Mental retardation	X-linked		Yes	Angelman Methylation UBE3A			N/A	Yes	Yes
OFD1	Oral-facial-digital syndrome 1; Joubert syndrome 10	X-linked	N/A	Yes	N/A	N/A	N/A	N/A	Yes	N/A

Table S3. Positive WES Cases

	Age	Gender	Gene	Mutation Type*	Mutation Origin	Associated Phenotype/Syndrome	Inheritance
1	37.9	F	*CRYGD*	HTZ nonsense†	Unknown‡	Cataract	AD
2	0.4	M	*CHD7*	HTZ splicing†	*de novo*	CHARGE	AD
3	3.9	F	*HDAC8*	HTZ missense†	*de novo*	Cornelia de Lange	AD
4	Fetus	U	*NIPBL*	HTZ splicing§	*de novo*	Cornelia de Lange	AD
5	17.2	F	*COL3A1*	HTZ missense§	*de novo*	Ehlers-Danlos type 4	AD
6	2.7	M	*SCN8A*	HTZ missense§	*de novo*	Epileptic encephalopathy, early infantile,	AD
7	15.1	F	*SRCAP*	HTZ nonsense§	*de novo*	Floating-Harbor	AD
8	0.3	F	*KAT6B*	HTZ 4-nt deletion§	Unknown‡	Genitopatellar	AD
9	9.8	M	*MLL2*	HTZ missense†	Inherited from symptomatic mother	Kabuki	AD
10	16.5	F	*FGFR1*	HTZ missense†	Inherited from symptomatic father	Kallman	AD
11	20.0	F	*ANKRD11*	HTZ 4-nt deletion§	*de novo*	KBG	AD
12	9.8	M	*ANKRD11*	HTZ missense§	*de novo*	KBG	AD
13	7.5	F	*KANSL1*	HTZ 1-nt deletion§	*de novo*	Mental retardation, AD, 17	AD
14	2.2	M	*SYNGAP1*	HTZ nonsense§	*de novo*	Mental retardation, AD, 5	AD
15	18.5	M	*DYRK1A*	HTZ nonsense§	*de novo*	Mental retardation, autism	AD

16	1.7	F	*KIF1A*	HTZ missense§	*de novo*	Mental retardation, AD, 9	AD
17	6.3	M	*ARID1A*	HTZ missense§	*de novo*	Mental retardation, Coffin Siris	AD
18	2.7	M	*ARID1B*	HTZ nonsense§	*de novo*	Mental retardation, Coffin Siris	AD
19	7.1	F	*ARID1B*	HTZ 13-nt deletion§	*de novo*	Mental retardation, Coffin Siris	AD
20	6.0	F	*SMARCB1*	HTZ missense§	*de novo*	Mental retardation, Coffin Siris	AD
21	3.8	F	*ZEB2*	HTZ 17-nt deletion§	Unknown‡	Mowat-Wilson	AD
22	3.3	F	*PTPN11*	HTZ missense†	Unknown‡	Noonan ; LEOPARD	AD
23	13.1	M	*KRAS*	HTZ missense†	Unknown‡	Noonan ; CFC	AD
24	16.5	M	*KRAS*	Mosaic missense§	*de novo*	Noonan ; CFC	AD
25	5.9	M	*CBL*	HTZ splicing§	*de novo*	Noonan -like	AD
26	9.9	F	*SHANK3*	HTZ splicing§	*de novo*	Phelan-McDermid	AD
27	3.0	M	*PTEN*	HTZ missense†	Inherited from symptomatic father	PTEN hamartoma tumor ; Macrocephaly/autism	AD
28	2.5	F	*CREBBP*	HTZ missense§	*de novo*	Rubinstein-Taybi	AD
29	5.3	M	*EP300*	HTZ 4-nt deletion§	*de novo*	Rubinstein-Taybi 2	AD
30	4.5	M	*ATL1*	HTZ missense†	Inherited from symptomatic father	Spastic Paraplegia 3	AD
31	16.2	M	*ATL1*	HTZ missense†	Unknown‡	Spastic Paraplegia 3	AD
32	6.3	M	*SPAST*	HTZ missense§	*de novo*	Spastic paraplegia 4	AD
33	3.9	M	*ITPR1*	HTZ missense§	*de novo*	Spinocerebellar ataxia 15	AD

34	0.5	M	*SCN2A* *POMT2*	SCN2A: HTZ missense§ HMZ missense‖	SCN2A: *de novo* POMT2: inherited, *in trans*	1) Seizures 2) Muscular dystrophy-dystroglycanopathy	AD AR
35	2.8	F	*SETBP1* *CLCN1*	SETBP1: HTZ missense† CLCN1: HTZ nonsense and missense‖	SETBP1: *de novo* CLCN1: Inherited, *in trans*	1) Schinzel-Giedion 2) Myotonia congenita	AD AR
36	0.2	F	*WDR19*	HTZ 1-nt deletion and missense§	Inherited, *in trans*	Asphyxiating thoracic dystrophy 5	AR
37	12.6	F	*SLC19A3*	HTZ 1-nt and 2-nt duplication§	Inherited, *in trans*	Biotin- or thiamine-responsive encephalopathy type 2	AR
38	2.1	M	*FBNL5*	HMZ 2-nt deletion§	mother is HTZ, father is not available	cutis laxa autosomal recessive type 1	AR
39	5.0	F	*STRC*	Apparently HMZ nonsense§	mother is HTZ, father is not available	Deafness autosomal recessive type 16	AR
40	14.6	M	*PRKRA*	HTZ missense mutations†§	Inherited, *in trans*	Dystonia 16	AR
41	1.7	M	*COL7A1*	HTZ missense and splicing†	Inherited, *in trans*	Epidermolysis bullosa dystrophica	AR
42	8.0	M	*GAN*	HTZ splicing and missense§	Inherited, *in trans*	Giant axonal neuropathy	AR
43	4.8	M	*GLB1*	HTZ missense mutations†	Inherited, *in trans*	GM1-gangliosidosis, Mucopolysaccharidosis type IVB	AR
44	6.8	F	*KIF7*	HTZ missense mutations‖	Inherited, *in trans*	Joubert type 12	AR
45	4.2	F	*C5orf42*	HTZ missense mutations§	Inherited, *in trans*	Joubert type 17	AR

46	2.2	F	*PEX1*	HTZ missense† and HTZ 1-nt duplication§	Inherited, *in trans*	Peroxisome biogenesis disorder complementation group 1	AR
47	0.8	M	*PNPO*	HMZ missense§	mother is HTZ, father is not available	Pyridoxamine 5'-phosphate oxidase deficiency	AR
48	3.3	F	*HIBCH*	HTZ splicing and missense§	Inherited, *in trans*	3-hydroxyisobutyryl-CoA hydrolase deficiency	AR
49	14.7	M	*NDUFV1*	HMZ missense†	Unknown‡	Mitochondrial complex I deficiency	AR
50	16.0	F	*SACS*	HTZ nonsense and 2-nt deletion§	Inherited, *in trans*	Spastic ataxia, Charlevoix-Saguenay	AR
51	4.0	F	*SACS*	HMZ 2-nt deletion§	Inherited	Spastic ataxia, Charlevoix-Saguenay	AR
52	9.1	M	*RAPSN* *ABCC9*	RAPSNAB: HTZ missense† ABCC9: HTZ indel†	*RAPSNAB*: Inherited, *in trans* *ABCC9*: inherited from mother	Congenital myasthenic syndrome Cardiomyopathy dilated type 1O	AR AD
53	3.7	M	*TREX1,* *PHEX*	TREX1: HTZ missense and 3-nt duplication† PHEX: hemizygous splicing§	*TREX1*: Inherited, *in trans* *PHEX*: inherited from symptomatic mother	1) Aicardi-Goutieres 2) Hypophosphatemic rickets	AR X-linked
54	0.1	M	*MTM1*	Hemizygous missense†	Inherited from mother	X-linked centronuclear myopathy	X-linked
55	4.1	M	*ATRX*	Hemizygous missense†	Inherited from mother	Alpha-thalassemia/mental retardation	X-linked

56	2.2	M	*ATRX*	Hemizygous 1-nt deletion§	Mother is mosaic	Alpha-thalassemia/mental retardation	X-linked
57	4.4	F	*SMC1A*	HTZ missense§	*de novo*	Cornelia de Lange	X-linked
58	0.3	M	*OFD1*	Hemizygous 6-nt deletion§	Inherited from the mother	Joubert 10	X-linked
59	2.4	M	*CASK*	Mosaic 2-nt duplication†	*de novo*	Mental retardation	X-linked
60	2.9	F	*OFD1*	HTZ 4-nt deletion§	*de novo*	Oral-facial-digital 1; Joubert 10	X-linked
61	1.4	M	*MECP2*	Hemizygous 1-nt deletion†	Unknown‡	Rett ; Severe neonatal encephalopathy	X-linked
62	0.6	M	*RBM10*	Hemizygous splicing§	*de novo*	TARP	X-linked

*** HTZ denotes heterozygous and HMZ homozygous**

† Mutation(s) previously reported in patients

‡ Parental samples are not available

§ Novel mutation(s)

ǁ Mutation(s) reported in 1000 Genome Project or ESP5400 databases with minor allele frequencies (MAF) less than 0.1%

Table S4. Medically Actionable Mutations Detected in the 250 Patients

Gene	Mutation	Disease
ABCC6	p.R1459C	Arterial calcification, generalized, of infancy, 2 [MIM:614473]; Pseudoxanthoma elasticum [MIM:264800]; Pseudoxanthoma elasticum, forme fruste [MIM:177850]
ACTA2	p.R39C	Aortic aneurysm, familial thoracic 6 [MIM:611788]
APC	p.S2685fs	Adenomatous polyposis coli [MIM:175100]; Desmoid disease, hereditary [MIM:135290]
CLCN1	p.R894X (n =2)	Myotonia congenita, dominant [MIM:160800]; Myotonia congenita, recessive [MIM:255700];
CPOX	p.R447C	Coproporphyria [MIM:121300]
DSG2	p.E1020fs	Arrhythmogenic right ventricular dysplasia 10 [MIM:610193]; Cardiomyopathy, dilated, 1BB [MIM:612877]
DSP	p.Q90R	Arrhythmogenic right ventricular dysplasia 8 [MIM:607450]; Dilated cardiomyopathy with woolly hair and keratoderma [MIM:605676]
DSP	p.V30M (n=3)	Arrhythmogenic right ventricular dysplasia 8 [MIM:607450]; Dilated cardiomyopathy with woolly hair and keratoderma [MIM:605676]
FBN1	p.R2726W (n=2)	Marfan syndrome [MIM:154700]; Aortic aneurysm, ascending, and dissection; Ectopia lentis, familial [MIM:129600]

FBN1	p.R1170H (n=2)	Marfan syndrome [MIM:154700]; Aortic aneurysm, ascending, and dissection; Ectopia lentis, familial [MIM:129600]
G6PD	p.S188F (n=2)	Hemolytic anemia due to G6PD deficiency [MIM:305900]
GPD1L	p.I124V	Brugada syndrome 2 [MIM:611777]
LDLR	p.G20R (n=3)	Hypercholesterolemia, familial [MIM:143890]; LDL cholesterol level QTL2 [MIM:143890]
MSH6	p.F1104fs	Colorectal cancer, hereditary nonpolyposis, type 5 [MIM:614350]
PKP2	p.S140F (n=2)	Arrhythmogenic right ventricular dysplasia, familial, 9 [MIM: 609040]
SCN5A	p.G298S	Atrial fibrillation, familial, 10 [MIM:614022]; Brugada syndrome 1 [MIM:601144]; Cardiomyopathy, dilated, 1E [MIM:601154]; Heart block, nonprogressive [MIM:113900]; Heart block, progressive, type IA [MIM:113900];Long QT syndrome-3 [MIM:603830]; Sick sinus syndrome 1 [MIM:608567]; Ventricular fibrillation, familial, 1 [MIM:603829]
SLC9A3R1	p.E225K	Nephrolithiasis/osteoporosis, hypophosphatemic, 2 [MIM:612287]
TTN	p.K2186fs	Cardiomyopathy, dilated, 1G [MIM:604145]; Cardiomyopathy, familial hypertrophic, 9 [MIM:613765]
TTN	p.Y9094X	Cardiomyopathy, dilated, 1G [MIM:604145]; Cardiomyopathy, familial hypertrophic, 9 [MIM:613765]
TTN	p.Q7040fs	Cardiomyopathy, dilated, 1G [MIM:604145]; Cardiomyopathy, familial hypertrophic, 9 [MIM:613765]

Table S5. Carrier Status in the 250 Patients in Genes from ACMG Recommended Population Screening Panel

Gene	Mutation	Disease
CFTR	p.F508del (n=3)	Cystic fibrosis [MIM:219700]; Congenital bilateral absence of vas deferens [MIM:277180]
CFTR	p.G551D	Cystic fibrosis [MIM:219700]; Congenital bilateral absence of vas deferens [MIM:277180]
CFTR	p.G622D (n=2)	Cystic fibrosis [MIM:219700]; Congenital bilateral absence of vas deferens [MIM:277180]
CFTR	p.R117H	Cystic fibrosis [MIM:219700]; Congenital bilateral absence of vas deferens [MIM:277180]
CFTR	p.R31C (n=2)	Cystic fibrosis [MIM:219700]; Congenital bilateral absence of vas deferens [MIM:277180]
GBA	p.N409S	Gaucher disease, perinatal lethal [MIM:608013]; Gaucher disease, type I [MIM:230800]; Gaucher disease, type II [MIM:230900]; Gaucher disease, type III [MIM:231000]; Gaucher disease, type IIIC [MIM:231005]
HEXA	c.1073+1G>A	GM2-gangliosidosis, several forms [MIM:272800]; Tay-Sachs disease [MIM:272800]
HEXA	p.D258H	GM2-gangliosidosis, several forms [MIM:272800]; Tay-Sachs disease [MIM:272800]
HEXA	p.S426fs	GM2-gangliosidosis, several forms [MIM:272800]; Tay-Sachs disease [MIM:272800]

Bioinformatic Resources for Data Analysis and Interpretation

Mercury Data Analysis Pipeline

The Mercury data analysis pipeline can be accessed at the following website: www.tinyurl.com/HGSC-Mercury. A quick-start guide is also available at: https://www.hgsc.bcm.edu/software/mercury. It requires a UNIX system.

Variant Filtering and Annotation

Variant annotation on an exome-wide scale is facilitated by a program developed by the Human Genome Sequencing Center called CASSANDRA, which describes the quality and predicted functional consequences of genomic variants, providing the biological and clinical contexts needed to assess the significance of each variant. Variants are presented to the interpretation team with all quality control metrics produced by the Atlas programs (Atlas-SNP and Atlas-Indel), the sequence data and the theoretical mappability (a measure of sequence degeneracy throughout the region) of the position. AnnoVar (Functional annotation of genetic variants from high-through-put sequencing data; www.openbioinformatics.org) is used to determine a variant's effect on both a conservative (RefSeq, NCBI Reference Sequence Database) and inclusive (University of California Santa Cruz Genome Browser) gene model set. This assessment also describes whether a variant changes an amino acid residue, whether it creates or removes a stop-codon, and the variant's location: near an intron-exon boundary, within an intron, within a known non-coding RNA, or in an intergenic region. The annotation also includes publically available algorithms that predict the deleterious nature of nonsynonymous variants [such as SIFT and PolyPhen]. Variants are additionally annotated according to their frequency and presence in multiple publically available variant collections (e.g., dbSNP Short Genetic Variations, 1000 Genomes Project, NHLBI GO Exome Sequencing Project) and the professional version of Human Gene Mutation Database (HGMD). Lastly, variants are annotated based on functional data for the gene in which they occur. These data include the known function of the gene (e.g., UniProtKB Swiss-Prot; www.ebi.ac.uk/uniprot), any previous association of the gene with a disease (e.g., Online Mendelian Inheritance in Man; www.omim.org), post-translational modifications of the gene, and the expression profile of the gene across human organs. Together, these data are applied to assess the variant quality, its minor allele frequency, and any disease association.