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Supplemental Data

PIK3R1 Mutations Cause Syndromic

Insulin Resistance with Lipoatrophy

Christel Thauvin-Robinet, Martine Auclair, Laurence Duplomb, Martine Caron-Debarle, Magali Avila, Judith St-Onge, Martine Le Merrer, Bernard Le Luyer, Delphine Héron, Michèle Mathieu-Dramard, Pierre Bitoun, Jean-Michel Petit, Sylvie Odent, Jeanne Amiel, Damien Picot, Virginie Carmignac, Julien Thevenon, Patrick Callier, Martine Laville, Yves Reznik, Cédric Fagour, Marie-Laure Nunes, Jacqueline Capeau, Olivier Lascols, Frédéric Huet, Laurence Faivre, Corinne Vigouroux, and Jean-Baptiste Rivière

Table S1. Summary of the Trio-Based Exome Sequencing Experiment

Family	Individual	Sequencing Output (in Gb)	Mean Sequencing Depth (Median)	Percent Target ≥10×	Total Variants[a]	NS/SS/I Variants[a]	Candidate De Novo Events
Trio 1	P1	5.1	63 (50)	87.1	36,858	9,580	4
	mother	4.1	50 (40)	85.0	-	-	-
	father	5.1	63 (50)	87.2	-	-	-
Trio 2	P2	4.9	61 (48)	86.8	28,598	9,839	4
	mother	4.7	60 (48)	86.5	-	-	-
	father	5.0	63 (49)	87.0	-	-	-

Gb, gigabases; NS/SS/I, nonsynonymous changes, splice-site variants and insertions/deletions.

[a]Variants that passed on the Genome Analysis Toolkit (GATK) hard-filtering parameters used for variant calling. Sequencing depth and coverage metrics were calculated using the GATK Depth of Coverage tool by considering only reads with mapping quality ≥ 20 and bases with base quality ≥ 20.[1]

Table S2. Candidate De Novo Events Identified in Subjects 1 and 2 (P1 and P2)

Coordinates (hg19)	Alleles (Ref/Alt)	Gene	Type of Change	Amino Acid Change	Proband Reads[a]	Father Reads[a]	Mother Reads[a]	Sanger Validation
P1								
chr4:3133452	C/T	*HTT*	missense	p.Ser729Phe	32/64	0/45	0/37	not tested
chr4:72120957	G/A	*SLC4A4*	missense	p.Gly32Arg	9/19	0/30	0/18	not tested
chr5:67591018	AATT/A	*PIK3R1*	in-frame del	p.Ile539del	14/26	0/18	0/23	de novo
chr12:48919883	C/A	*OR8S1*	missense	p.Leu157Ile	87/249	0/250	2/240	not tested
P2								
chr5:60628574	CCGGCCGCAACCTCGG/C	*ZSWIM6*	in-frame del	-	2/10	0/5	0/7	not tested
chr5:67590403	G/A	*PIK3R1*	missense	p.Glu489Lys	19/56	1/52	0/44	de novo
chr15:65678327	C/CA	*IGDCC4*	frameshift ins	-	3/9	0/8	0/8	not tested
chr17:72878822	C/T	*FADS6*	missense	p.Ala126Thr	13/27	0/36	0/24	not tested

Ref, reference allele; alt, alternative allele; del, deletion; ins, insertion. [a]The numerator indicates the number of reads supporting the variant; the denominator indicates the total number of reads at the variant site. The nomenclature of *PIK3R1* mutations is based on RefSeq accession number NM_181523.2. None of the two index individuals had likely disease-causing mutations in *AGPAT2*, *BSCL2*, *LMNA*, *PPARG* or *INSR*.

Table S3. Main Clinical Features of the 14 Additional Affected Individuals Tested for *PIK3R1* Mutations

Individual	Features of the SHORT Acronym					Other Findings			
	Short Stature	Hyperextensibility of Joints or Inguinal Hernia	Ocular Depression	Rieger Anomaly	Teeth Delay	Facial Dysmorphism	Lipoatrophy	Diabetes	Additional Findings
P7	-	-	NA	-	+	+	+	+	astigmatism, brachydactyly, severe insulin resistance, primary amenorrhea due to polycystic ovary syndrome
P8	+	-	+	-	NA	+	+	+	severe insulin resistance
P9	+	-	-	-	NA	+	+	+	hemiparesis and intellectual disability secondary to neonatal cerebral hemorrhage
P10	+	-	-	NA	NA	+	+	+	severe insulin resistance, acanthosis nigricans, hirsutism, hypomastia
P11	+	-	NA	NA	NA	+	+	+	severe insulin resistance
P12	+	-	-	NA	NA	+	+	-	acanthosis nigricans, hypertrophic cardiomyopathy, hepatomegaly
P13	+	-	-	NA	+	+	+	+	severe insulin resistance, primary amenorrhea
P14	+	-	-	NA	NA	+	+	+	acanthosis nigricans, insulin resistance, deafness
P15	-	-	-	-	-	+	+	-	congenital bilateral cataract, iris atrophy, hepatomegaly, alopecia, myopathy
P16	+	-	-	NA	NA	+	+	+	severe insulin resistance, liver steatosis, hypertriglyceridemia
P17	+	-	-	-	-	+	+	-	moderate hyperopia
P18	-	-	-	+	-	+	+	-	oligodontia
P19	+	-	-	-	+	+	+	-	aortic valve stenosis, hypospadias, micropenis
P20	-	-	-	-	-	+	+	+	

NA, not available.

Table S4. Allele Frequency of the Five *PIK3R1* Mutation Sites Associated with SHORT Syndrome in ~6,500 Individuals from the NHLBI GO Exome Sequencing Project

Mutation Coordinates (hg19)	Alleles (Ref/Alt)	cDNA Change	dbSNP ID	European American Allele Count (Alt/Ref)	African American Allele Count (Alt/Ref)	All Allele Count (Alt/Ref)	Average Sample Read Depth
chr5:67591018	AATT/A	c.1615_1617delATT	none	0/8600	0/4406	0/1306	102
chr5:67590403	G/A	c.1465G>A	none	0/8600	0/4406	0/1306	66
chr5:67592129	C/T	c.1945C>T	none	0/8600	0/4406	0/1306	161
chr5:67592127	T/TT	c.1943dupT	none	0/8600	0/4406	0/1306	162
chr5:67592076	G/A	c.1892G>A	none	0/8600	0/4406	0/1306	179

Ref, reference allele; alt, alternative allele. The nomenclature of *PIK3R1* mutations is based on RefSeq accession number NM_181523.2. The NHLBI Exome Sequencing Project (ESP) dataset consists of deep-coverage whole-exome data from ~6,500 subjects (13,000 chromosomes; see Web Resources).

Table S5. Detailed Endocrine and Biological Data in Eight Individuals with *PIK3R1* Mutations

		Subject								
		P1[a]	**P2**[a]	**P3**		**P4**	**P5**	**P7**	**P8**	**P9**
Age		7y 9m	7y 8m	11y 6m	13y 6m	20m	40y	28y	60y	28y
Glycated hemoglobin (N = 4.0–6.0%)		5.4	5.2	7.3	7.7	NA	9.0	6.8	8.0	6.1
Serum IgF1 (N = 57–316ng/ml)		296	NA	NA	NA	NA	NA	285	NA	NA
Oral glucose tolerance test										
T0	Blood glucose level (N < 6.1 mmol/l)	4.49	5.06	4.9	10.5	NA	11.6	8.6	12.0	6.1
	Serum insulin (N < 20 mUI/l)	38.3	52.0	69	56	NA	NA	12	76	23
	Peptide C (0.5–3.0 ng/ml)	4.9	7.0	NA	NA	NA	NA	2.7	13.3	8.5
T30	Blood glucose level (mmol/l)	8.78	9.02	8.5	16.9	NA	NA	17	NA	NA
	Serum insulin (mUI/l)	284.0	929.0	>300	82.7	NA	NA	37	NA	NA
	Peptide C (ng/ml)	20.2	45.8	NA	NA	NA	NA	5.2	NA	NA
T60	Blood glucose level (N < 11.1 mmol/l)	6.34	NA[b]	7.1	21	NA	NA	21	NA	NA
	Serum insulin (mUI/l)	211.0	NA[b]	>300	169	NA	NA	40	NA	NA
	Peptide C (ng/ml)	15.3	NA[b]	NA	NA	NA	NA	7.8	NA	NA
T120	Blood glucose level (N < 7.8 mmol/l)	6.55	6.6	6.9	18.5	NA	NA	24	NA	NA
	Serum insulin (mUI/l)	228.0	240.0	>300	146	NA	NA	76	NA	NA
	Peptide C (ng/ml)	16.3	17.2	NA	NA	NA	NA	10.6	NA	NA
T180	Blood glucose level (mmol/l)	5.87	3.68	5.3	12.4	NA	NA	23	NA	NA
	Serum insulin (mUI/l)	98.8	53.8	207	76.9	NA	NA	158	NA	NA
	Peptide C (ng/ml)	14.5	5.1	NA	NA	NA	NA	15.5	NA	NA
Serum triglycerides (N = <1.7mmol/l)		0.44	0.55	1.32	NA	0.68	0.66	1.98	2.10	1.99
Serum total cholesterol (N = 3.10–5.20mmol/l)		3.03	3.70	3.82	NA	4.69	3.77	4.43	4.13	7.4
HDL-cholesterol (N = 0.90–1.60mmol/l)		1.25	1.62	NA	NA	1.22	1.11	0.88	0.93	1.54
Leptin (N = 0.80–3.20ng/ml))		1.41	<1.00	NA	NA	NA	NA	NA	NA	<1.00
Adiponectin (N = 3.8–11.8µg/ml)		11.0	NA	NA	NA	NA	NA	NA	NA	9.13
Serum IgA level (N = 0.56–1.38g/l)		0.85	0.65	NA	NA	<0.26	NA	NA	NA	NA
Serum IgG level (N = 6.8–10.2g/l)		6.6	7.1	NA	NA	10.7	NA	NA	NA	NA
Blood calcium (N = 2.12–2.52 mmol/l)		2.13	2.38	2.48	NA	2.5	2.42	2.19	2.34	2.47

Y, year; m, month; NA, not available.
[a]These subjects were under growth hormone treatment during the course of the evaluation.
[b]Not available because of hemolysis.

Reference

1. McKenna, A., Hanna, M., Banks, E., Sivachenko, A., Cibulskis, K., Kernytsky, A., Garimella, K., Altshuler, D., Gabriel, S., Daly, M., et al. (2010). The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res. *20*, 1297-1303.