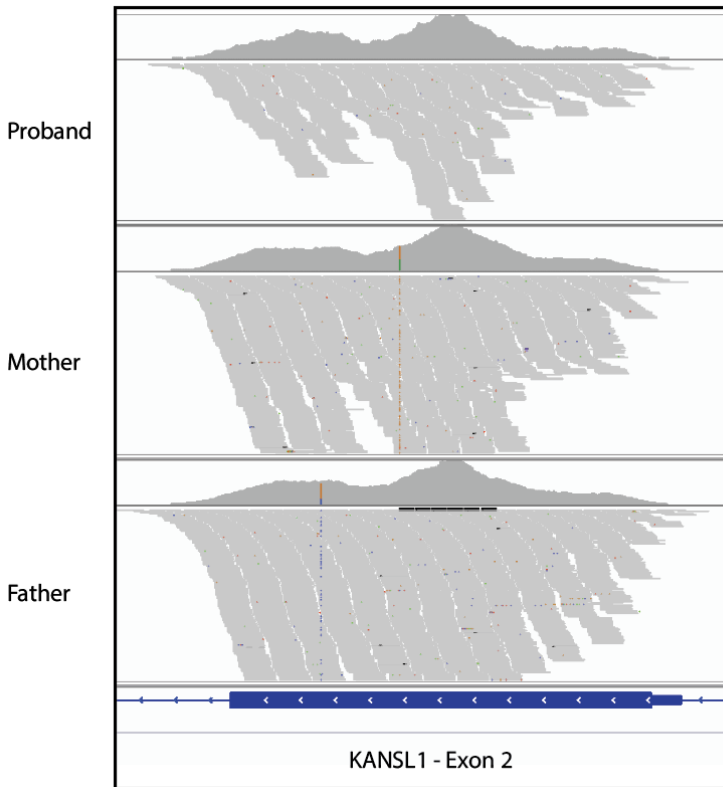
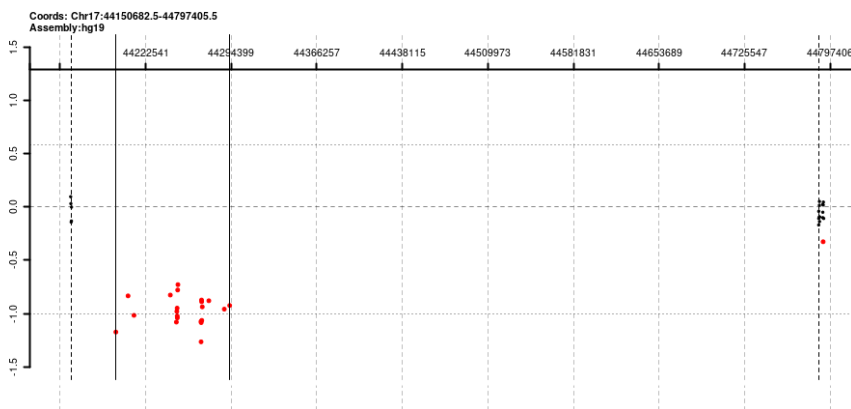


Supplemental Material

A



B



Supplemental Figure 1. Case 3 - Koolen-de Vries syndrome. (A) ES coverage plot showing decreased read depth of *KANSL1* exon 2 in proband compared to parents suggestive of a deletion. **(B)** CMA shows evidence of *KANSL1* deletion interpreted as benign due to other similar losses having been seen in the ClinVar and Decipher and reported as benign.

Supplemental Table 1. Gene expression statistics by disease gene category and tissue type.

Gene Class (N)	Proportion of Genes with TPM > 10			TPM (Mean)		TPM (Standard Deviation)	
	FB	WB	p-value	FB	WB	FB	WB
Aortopathy (25)	0.8	0.24	< 1E-10	452.5	12.2	1188.4	34.4
Mitochondrial (Nuclear) (202)	0.74	0.25	< 1E-10	42.3	12.4	90.5	40.1
Neuropathy (72)	0.66	0.27	< 1E-10	49.8	12.4	89.6	35.9
Retinal Dystrophy (8)	0.62	0.25	< 1E-10	16.6	5.5	13.5	5.9
Skeletal Dysplasia (47)	0.6	0.15	< 1E-10	713.5	10.9	3078.4	36.9
Autism/Intellectual Disability (104)	0.58	0.25	< 1E-10	20.1	7	27	11.4
Cancer (84)	0.58	0.25	< 1E-10	66.7	7.8	408.2	13.8
Inborn Errors of Metabolism (93)	0.57	0.16	< 1E-10	22.8	6.4	31.7	11
Central Nervous System Malformation (103)	0.53	0.13	< 1E-10	123.6	34.8	604.3	247.8
Congenital Heart Defect (42)	0.51	0.22	< 1E-10	42.5	6.2	141	16
OMIM Disease Genes (4218)	0.46	0.22	< 1E-10	66.3	185.9	1187	7337.9
Immunodeficiency (207)	0.45	0.58	< 1E-10	45.3	56.8	322.5	206.7
Cardiomyopathy (50)	0.44	0.14	< 1E-10	43.3	6.1	89.6	17.1
Epilepsy (146)	0.42	0.15	< 1E-10	18.4	6.7	52.4	23.4
Exome (19488)	0.4	0.2	< 1E-10	38.3	49.8	578.9	3441.3
Arrhythmia (39)	0.23	0.18	< 1E-10	60.2	12.9	203.9	41.1

FB: Fibroblasts, WB: Whole Blood, TPM: Transcripts per million. The disease-gene lists were based on panels available from GeneDx and Invitae. OMIM disease genes were downloaded directly from <https://omim.org/downloads> in February 2020. Protein-coding RefSeq genes constituted the exome gene list.

Supplemental Table 2. Gene expression by tissue for RNA-seq diagnosed cases.

Diagnosis (Dx)	Gene	Sampled Tissue(s)	Fibroblast Expression (TPM)	Blood Expression (TPM)
Renpenning syndrome	<i>PQBP1</i>	Blood	45.4	30.8
<i>CLTC</i> -associated ID syndrome	<i>CLTC</i>	Fibroblast, Blood	185.7	26.5
Koolen-de Vries syndrome	<i>KANSL1</i>	Fibroblast	11.1	8.6
Dopa Responsive Dystonia	<i>SPR</i>	Fibroblast	34.2	1.6
<i>NSD2</i> -associated ID syndrome	<i>NSD2</i>	Fibroblast, Blood	16.4	1.4
<i>CHASERR</i> -associated syndrome	<i>CHASERR</i>	Fibroblast	20.6	21.8
Brachydactyly syndrome, type B	<i>ROR2</i>	Fibroblast, Blood	9.8	0.02
<i>TBCK</i> -associated Syndromic Encephalopathy	<i>TBCK</i>	Fibroblast	11	0.9
<i>RPL13</i> -associated SEMD	<i>RPL13</i>	Fibroblast	718.2	319.4
<i>PRUNE1</i> -associated DD syndrome	<i>PRUNE1</i>	Fibroblast	10.9	9.2
Noonan-like syndrome	<i>LZTR1</i>	Fibroblast, Blood	34.5	11.1
Noonan-like syndrome	<i>LZTR1</i>	Fibroblast, Blood	34.5	11.1
Au-Kline syndrome	<i>HNRNPK</i>	Fibroblast, Blood	520.6	193
Spastic paraplegia 50	<i>AP4M1</i>	Fibroblast	15.3	2.87

Gene expression values in transcripts per million (TPM) according to GTEx for the presented cases solved with RNA-seq. DD – developmental delay, ID – intellectual disability, SEMD – spondyloepimetaphyseal dysplasia

Supplemental Table 3. Gene expression and splicing outlier counts.

Outlier Category	FB Counts (SD)	WB Counts (SD)
High/Low Expression Genes	2.79 (3.11)	3.88 (9.12)
High/Low Expression Genes, OMIM Disease	0.72 (1.16)	0.94 (2.35)
Low Expression Genes, pLI \geq 0.9 or DOMINO \geq 0.8	0.35 (0.83)	0.18 (0.43)
Low Expression Genes, pLI \geq 0.9 or DOMINO \geq 0.8, OMIM Disease	0.11 (0.34)	0.09 (0.29)
Novel Splicing Events (\leq 2 Samples Per Junction)	60.7 (51.7)	22.5 (24.8)
Novel Splicing Events (\leq 2 Samples Per Junction), OMIM Disease	26.4 (22.9)	6.56 (7.28)

FB: Fibroblasts, WB: Whole Blood, SD: Standard Deviation. Counts represent the average number of genes or novel splicing events per proband in each category for respective tissues.

Members of the Undiagnosed Diseases Network

Maria T. Acosta
Margaret Adam
David R. Adams
Pankaj B. Agrawal
Mercedes E. Alejandro
Justin Alvey
Laura Amendola
Ashley Andrews
Euan A. Ashley
Mahshid S. Azamian
Carlos A. Bacino
Guney Bademci
Eva Baker
Ashok Balasubramanyam
Dustin Baldrige
Jim Bale
Michael Bamshad
Deborah Barbouth
Pinar Bayrak-Toydemir
Anita Beck
Alan H. Beggs
Edward Behrens
Gill Bejerano
Jimmy Bennet
Beverly Berg-Rood
Jonathan A. Bernstein
Gerard T. Berry
Anna Bican
Stephanie Bivona
Elizabeth Blue
John Bohnsack
Carsten Bonnenmann
Devon Bonner
Lorenzo Botto
Brenna Boyd
Lauren C. Briere
Elly Brokamp
Gabrielle Brown
Elizabeth A. Burke
Lindsay C. Burrage
Manish J. Butte
Peter Byers
William E. Byrd
John Carey
Olveen Carrasquillo
Ta Chen Peter Chang
Sirisak Chanprasert
Hsiao-Tuan Chao
Gary D. Clark

Terra R. Coakley
Laurel A. Cobban
Joy D. Cogan
Matthew Coggins
F. Sessions Cole
Heather A. Colley
Cynthia M. Cooper
Heidi Cope
William J. Craigen
Andrew B. Crouse
Michael Cunningham
Precilla D'Souza
Hongzheng Dai
Surendra Dasari
Joie Davis
Jyoti G. Dayal
Matthew Deardorff
Esteban C. Dell'Angelica
Shweta U. Dhar
Katrina Dipple
Daniel Doherty
Naghmeh Dorrani
Argenia L. Doss
Emilie D. Douine
David D. Draper
Laura Duncan
Dawn Earl
David J. Eckstein
Lisa T. Emrick
Christine M. Eng
Cecilia Esteves
Marni Falk
Liliana Fernandez
Carlos Ferreira
Elizabeth L. Fieg
Laurie C. Findley
Paul G. Fisher
Brent L. Fogel
Irman Forghani
Laure Fresard
William A. Gahl
Ian Glass
Bernadette Gochuico
Rena A. Godfrey
Katie Golden-Grant
Alica M. Goldman
Madison P. Goldrich
David B. Goldstein
Alana Grajewski
Catherine A. Groden
Irma Gutierrez

Sihoun Hahn
Rizwan Hamid
Neil A. Hanchard
Kelly Hassey
Nichole Hayes
Frances High
Anne Hing
Fuki M. Hisama
Ingrid A. Holm
Jason Hom
Martha Horike-Pyne
Alden Huang
Yong Huang
Laryssa Huryn
Rosario Isasi
Fariha Jamal
Gail P. Jarvik
Jeffrey Jarvik
Suman Jayadev
Lefkothea Karaviti
Jennifer Kennedy
Dana Kiley
Isaac S. Kohane
Jennefer N. Kohler
Deborah Krakow
Donna M. Krasnewich
Elijah Kravets
Susan Korrick
Mary Koziura
Joel B. Krier
Seema R. Lalani
Byron Lam
Christina Lam
Grace L. LaMoure
Brendan C. Lanpher
Ian R. Lanza
Lea Latham
Kimberly LeBlanc
Brendan H. Lee
Hane Lee
Roy Levitt
Richard A. Lewis
Sharyn A. Lincoln
Pengfei Liu
Xue Zhong Liu
Nicola Longo
Sandra K. Loo
Joseph Loscalzo
Richard L. Maas
John MacDowall
Ellen F. Macnamara

Calum A. MacRae
Valerie V. Maduro
Marta M. Majcherska
Bryan C. Mak
May Christine V. Malicdan
Laura A. Mamounas
Teri A. Manolio
Rong Mao
Kenneth Maravilla
Thomas C. Markello
Ronit Marom
Gabor Marth
Beth A. Martin
Martin G. Martin
Julian A. Martínez-Agosto
Shruti Marwaha
Jacob McCauley
Allyn McConkie-Rosell
Colleen E. McCormack
Alexa T. McCray
Elisabeth McGee
Heather Mefford
J. Lawrence Merritt
Matthew Might
Ghayda Mirzaa
Eva Morava
Paolo M. Moretti
Deborah Mosbrook-Davis
John J. Mulvihill
David R. Murdock
Anna Nagy
Mariko Nakano-Okuno
Avi Nath
Stan F. Nelson
John H. Newman
Sarah K. Nicholas
Deborah Nickerson
Shirley Nieves-Rodriguez
Donna Novacic
Devin Oglesbee
James P. Orengo
Laura Pace
Stephen Pak
J. Carl Pallais
Christina GS. Palmer
Jeanette C. Papp
Neil H. Parker
John A. Phillips III
Jennifer E. Posey
Lorraine Potocki
Bradley Power

Barbara N. Pusey
Aaron Quinlan
Wendy Raskind
Archana N. Raja
Deepak A. Rao
Genecee Renteria
Chloe M. Reuter
Lynette Rives
Amy K. Robertson
Lance H. Rodan
Jill A. Rosenfeld
Natalie Rosenwasser
Francis Rossignol
Maura Ruzhnikov
Ralph Sacco
Jacinda B. Sampson
Susan L. Samson
Mario Saporta
C. Ron Scott
Judy Schaechter
Timothy Schedl
Kelly Schoch
Daryl A. Scott
Vandana Shashi
Jimann Shin
Rebecca Signer
Edwin K. Silverman
Janet S. Sinsheimer
Kathy Sisco
Edward C. Smith
Kevin S. Smith
Emily Solem
Lilianna Solnica-Krezel
Ben Solomon
Rebecca C. Spillmann
Joan M. Stoler
Jennifer A. Sullivan
Kathleen Sullivan
Angela Sun
Shirley Sutton
David A. Sweetser
Virginia Sybert
Holly K. Tabor
Amelia L. M. Tan
Queenie K.-G. Tan
Mustafa Tekin
Fred Telischi
Willia Thorson
Audrey Thurm
Cynthia J. Tiff
Camilo Toro

Alyssa A. Tran
Brianna M. Tucker
Tiina K. Urv
Adeline Vanderver
Matt Velinder
Dave Viskochil
Tiphonie P. Vogel
Colleen E. Wahl
Stephanie Wallace
Nicole M. Walley
Chris A. Walsh
Melissa Walker
Jennifer Wambach
Jijun Wan
Lee-kai Wang
Michael F. Wangler
Patricia A. Ward
Daniel Wegner
Mark Wener
Tara Wenger
Katherine Wesseling Perry
Monte Westerfield
Matthew T. Wheeler
Jordan Whitlock
Lynne A. Wolfe
Jeremy D. Woods
Shinya Yamamoto
John Yang
Muhammad Yousef
Diane B. Zastrow
Wadih Zein
Chunli Zhao
Stephan Zuchner