Somatic reversion events point towards *RPL4* as a novel disease gene in a condition resembling Diamond-Blackfan anemia

Marjolijn C. J. Jongmans,[1,2,3] Illja J. Diets,[1] Paola Quarello,[4] Emanuela Garelli,[5] Roland P. Kuiper[3] and Rolph Pfundt[1]

[1]Department of Human Genetics, Radboud university medical center and Radboud Institute for Molecular Life Sciences, Nijmegen, the Netherlands; [2]Department of Medical Genetics, University Medical Center Utrecht, the Netherlands; [3]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands; [4]Paediatric Onco-Haematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, Torino, Italy and [5]Department of Public Health and Paediatric Sciences, University of Torino, Italy

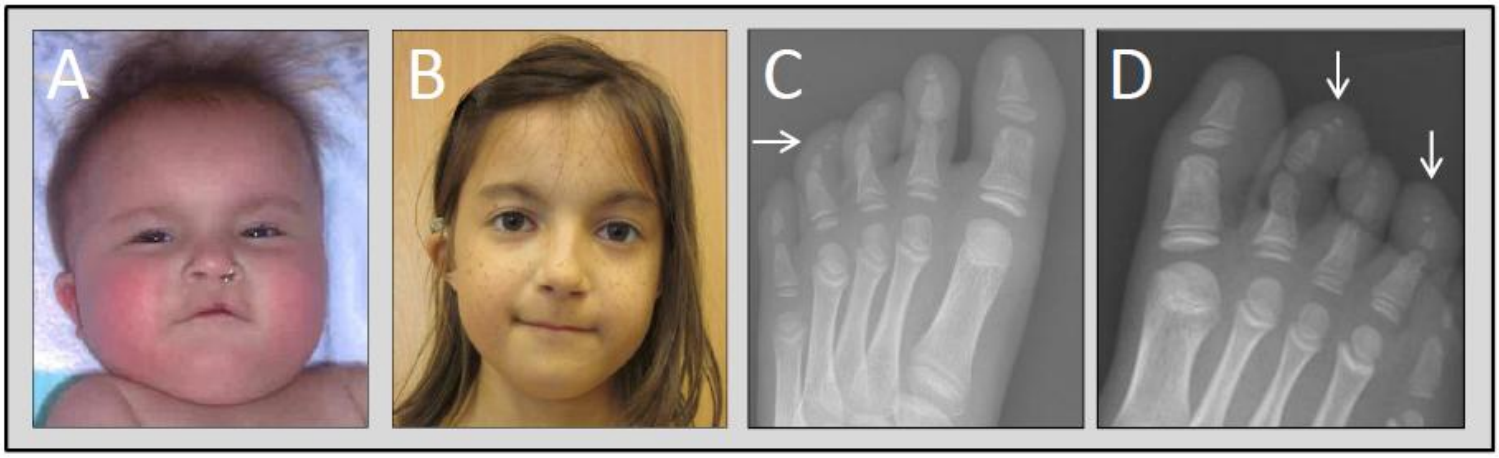
Correspondence: M.C.J.Jongmans-3@umcutrecht.nl
doi:10.3324/haematol.2018.200683

Supplementary Appendix

Somatic reversion events point towards *RPL4* as a novel disease gene in a condition resembling Diamond-Blackfan Anemia.

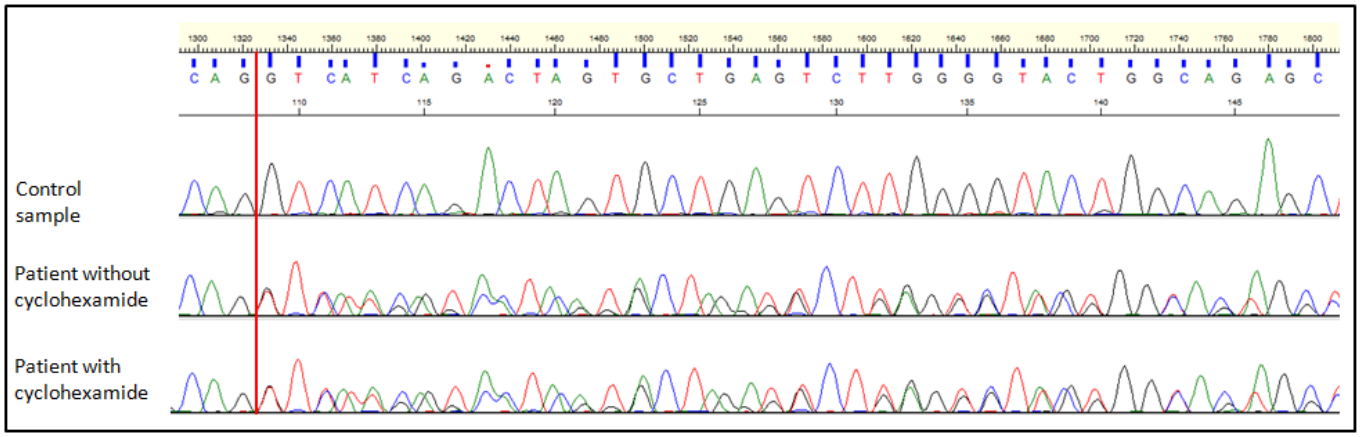
Marjolijn Jongmans[1,2,3], Illja J. Diets[1], Paola Quarello[4], Emanuela Garelli[5], Roland P. Kuiper[3], Rolph Pfundt[1]

1 Dept. of Human Genetics, Radboud university medical center and Radboud Institute for Molecular Life Science, Nijmegen, The Netherlands
2 Dept. of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands
3 Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
4 Paediatric Onco-Haematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, Torino, Italy
5 Department of Public Health and Paediatric Sciences, University of Torino, Torino, Italy



Supplementary Figure S1 – Clinical features of patient with *RPL4* mutation

The patient at age 8 months (A), and age 10 years old (B). Note the partial cleft lip and low set ears. X-rays of the feet (C,D) reveal shortening of the middle phalanges of the 2nd - 4th toe and duplication of the distal phalanges of these toes (duplication best seen at arrows).



Supplementary Figure S2 – cDNA sequencing analysis on RNA samples isolated from cultured fibroblasts.

cDNA sequencing on RNA isolated from cultured fibroblasts from a control sample and the patient. Both in the absence, and presence of cyclohexamide, the mutation results in a transcript containing an insertion of six nucleotides, indicating that it is not subjected to nonsense mediated decay.

Supplementary Table S1. OMIM genes in 15q UPD region					
OMIM gene	**Gene localization**	**Associated disease**	**Overlapping features with our patient**	**Inheritance**	**Mutations identified in exome sequencing data?**
EFTUD1	15q25.2	Shwachman-Diamond syndrome 2	Short stature, failure to thrive, hematopoietic abnormalities	AD	No
RPS17	15q25.2	Diamond-Blackfan anemia 4	Short stature, cleft lip, hematopoietic abnormalities	AD	No
WDR73	15q25.2	Galloway-Mowat syndrome 1	Delayed development, short stature	AR	No
FANCI	15q26.1	Fanconi anemia, complementation group I	Short stature, congenital anomalies, hematopoietic abnormalitie	AR	No
BLM	15q26.1	Bloom syndrome	Short stature, delayed development, congenital anomalies	AR	No
Abbreviations: UPD = uniparental disomy; AR = autosomal recessive; AD = autosomal dominant					

Supplementary Table S2. Variants identified in 15q UPD region							
Gene name	**Mutation**	**OMIM**	**PhyloP**	**In house frequency**	**gnomAD frequency**	**Allele frequency**	**Candidate gene?**
RPL4	c.176-7A>G p.(Ala58_Gly59insValLeu)	No associated disease, ribosomal gene	-	0	0	40%	Yes
NOX5	c.706G>A p.(Gly236Ser)	No associated disease, NADPH oxidase	3.116	0	0	37.5%	VUS
LARP6	c.355C>A p.(Val119Leu)	No associated disease	5.158	0	2.88E-05 (N=8)	30.5%	VUS
STRA6	c.2038A>C p.(Tyr680Asp)	Microphthalmia, isolated or syndromic (AR)	3.515	0	0	25%	No phenotype match
Abbreviations: UPD = uniparental disomy; AR = autosomal recessive; VUS = variant of unknown significance							