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Mosaic Variegated Aneuploidy Syndrome and Noonan Syndrome in the Same Family

Christian T. Hübner[a] Asmaa K. Amin[b] Daniela Dey[a] Robert Meyer[a] Thomas Eggermann[a]

[a]Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany; [b]Department of Human Genetics, Medical Research Institute, Alexandria University, Alexandria, Egypt

Established Facts

- Mosaic variegated aneuploidy syndrome 2 (MVA2) is a rare congenital disorder with only few reported cases.
- MVA2 and Noonan syndrome show overlapping phenotypes.
- In family members exhibiting similar features, the same clinical etiology is assumed.

Novel Insights

- A new pathogenic variant in *CEP57* is described, causing MVA2.
- The short stature phenotype in the family is caused by *CEP57* and *PTPN11* variants in the different patients. The different genetic disorders require a different therapeutic management in the family members.

Keywords
CEP57 · Molecular diagnostics · Mosaic variegated aneuploidy · Noonan syndrome · *PTPN11* · Whole exome sequencing

Abstract
Introduction: Mosaic variegated aneuploidy syndrome 2 (MVA2) and Noonan syndrome (NS) are 2 genetic disorders with overlapping clinical features, including intrauterine growth retardation, dysmorphic features, and heart defects. Whereas NS is a well-known congenital entity, MVA2 is rare, and only a few cases have been reported in the literature. ***Case Presentation:*** We report on the molecular findings in 3 patients with short stature phenotypes from the same family. By considering the clinical overlap between the patients, a common cause for the small stature was assumed in the beginning, but by whole exome analysis (WES) it turned out that the phenotypes were caused by different pathogenic variants in *CEP57* and *PTPN11*, respectively. As a result, both MVA2 and NS occurred in the same family. ***Conclusion:*** As our example shows, the parallel occurrence of pathogenic

C.T.H and A.K.A. contributed equally to this work.

Karger@karger.com
www.karger.com/msy

Correspondence to:
Thomas Eggermann, teggermann@ukaachen.de

Karger

alterations in different genes in the same family constitutes a challenge for the interpretation of WES data and has to be considered. The diagnostic workup illustrates the need for a careful anamnesis and molecular documentation in affected and healthy family members. The knowledge on the different molecular causes underlying the features of the affected family members is the basis for personalised therapeutic managements and can avoid unnecessary burden and even contraindicated therapies; while in patients with NS carrying *PTPN11* variants growth hormone treatment leads to height increase, patients with MVA2 carrying *CEP57* probably do not benefit from it.

Introduction

Mosaic variegated aneuploidy (MVA) syndrome and Noonan syndrome (NS) are 2 genetic disorders which are both characterized by short stature, dysmorphic features, and heart defects. Whereas NS is a well-known congenital entity, MVA syndrome is rare, and only a few cases have been reported in the literature. MVA is caused by autosomal recessive pathogenic variants in 3 different genes, *BUB1B* (MVA1 [OMIM 257300]), *CEP57* (MVA2 [OMIM 614114]), and *TRIP13* (MVA3 [OMIM 617598]) [Hanks et al., 2004; Snape et al., 2011; Yost et al., 2017]. Clinical features comprise intrauterine growth retardation (IUGR), postnatal short stature, rhizomelic shortening of upper and lower limbs, dysmorphic features, microcephaly, and normal or mildly delayed development [for review, see Santos-Simarro et al., 2021] (Table 1). Additionally, tumor predisposition is reported for MVA patients carrying variants in *BUB1B* and *TRIP13*, whereas for *CEP57* this association has not yet been reported [Dery et al., 2020].

NS (OMIM 163950) is an autosomal dominant syndrome and characterized by IUGR and short stature as well, additionally congenital heart defects, a typical facial gestalt and skeletal malformations are characteristic [Noonan et al., 1968; Tartaglia et al., 2002]. Meanwhile, 8 different genes associated with NS have been identified which are all involved in the RAS-MAPK-signaling pathway, making NS a clinically and molecularly heterogeneous disorder. Pathogenic variants in *PTPN11* cause up to 50% of clinical NS cases and are inherited in an autosomal dominant manner.

Here, we report 3 patients from the same family with overlapping phenotypes and molecular NS and MVA2, respectively (Table 1).

Case Report

The Egyptian patient II-7 was referred to genetic counselling because of severe growth restriction and facial dysmorphisms. His brother II-1 and his father I-1 also presented small stature and dysmorphic facial features (Fig. 1). In the family 8 pregnancies resulted in the 2 small statured boys (II-7 and II-1), in a healthy boy (II-5) and a healthy girl (II-8), 3 stillbirths (II-2, II-3, II-4) and 1 child dying perinatally (II-6) (Fig. 2).

Patient II-7/CEP57

Patient II-7 was born after an uneventful pregnancy at gestational week 39 by spontaneous delivery. Birth weight was 750 g (<1st percentile; −6.32 Z), birth length and head circumference were not reported. Early development of motor skills and intellect was normal, sitting was achieved at 6 months, crawling at 9 months and walking at 1 year of age. Postnatal growth was significantly reduced. Growth hormone treatment was started at the age of 6 years with only poor response. The boy was presented for genetic diagnosis at the age of 9 years and 5 months. At that time, height was 95 cm (<1st percentile; −6.85 Z), weight 14 kg (<1st percentile; −7.61 Z) and head circumference 46 cm (<1st percentile; −5.52 Z). He attended a regular school. Facial dysmorphisms included an oval asymmetric face, midface hypoplasia, small low set ears, slightly prominent eyes, a prominent nose, a high frontal hairlineand a small mouth with microretrognathia. Further clinical findings comprised small hands and feet, a clinodactyly V and skin hyperpigmentation including café-au-lait spots. Brain MR imaging was performed at 1.5 years and showed a deepening of cortical sulci.

Patients II-1 and I-1/PTPN11

Patient II-1 was the firstborn son of the family; he was born at term by vaginal delivery with a birth weight of 2 kg (<1st percentile; −3.68 Z). Motor and speech development were uneventful. A septal heart defect was surgically corrected at the age of 5 years. At the age of 15 years, height of 134 cm (<1st percentile; −4.79 Z), weigth of 32 kg (<1st percentile; −6.36 Z), and a head circumference of 51 cm (<1st percentile; −3.33 Z) were documented. Facial features included posteriorly rotated ears and a low posterior hairline. A webbed neck and downslanting palpebral fissures were reported as well (Fig. 1).

According to the family, the father I-1 was born with low birth weight. Measurement at investigation revealed a height of 146.5 cm (<1st percentile; −4.98 Z), weigth of 43 kg (<1st percentile; −4.26 Z), and a head circumference of 53 cm (<1st percentile; −2.65 Z). Clinical features were similar to patient II-1.

Material and Methods

Genomic DNA was extracted from peripheral blood lymphocytes using a salting out procedure. For whole exome sequencing (WES) of patients II-1 and II-7, exome capturing was conducted using the xGen™ Exome Research Panel v2 (IDT, Coralville, IA, USA) according to the manufacturer's protocol and sequenced on a NextSeq500 Sequencer with 2 × 75 cycles on a high-output flow cell (Illumina, San Diego, CA, USA). FastQ-files were generated with bcl2fastq2 (Illumina). Alignment and variant calling was per-

Table 1. Comparison of the clinical key features of *CEP57*-associated MVA2 and *PTPN11*-linked NS reported in the literature with those in presented family

	MVA2 syndrome[a]		*PTPN11*-associated NS[b]		Patient II-7, *CEP57* 9 5/12 years	Patient II-1, *PTPN11* 15 years	Patient I-1, *PTPN11* 37 years
	at birth	as child	at birth	as child			
Short stature	9/12	12/12	75%	40%	−6.85 Z (95 cm)	−4.79 Z (134 cm)	−4.98 Z (146.5 cm)
Weight					−7.61 Z (14 kg)	−6.36 Z (32 kg)	−4.26 Z (43 kg)
Head circumference					−5.52 Z (46 cm)	−3.33 Z (51 cm)	−2.65 Z (53 cm)
Prominent forehead	7/9		32%		+	+	Mild
Hypertelorism	1/12		50%		–	+	+
Ptosis	NR		55%		–	–	–
Downslanting palpebral fissures	NR		84%		Mild	+	+
Low set ears	8/12		67%		+	+	+
Micrognathia	8/12		NR		+	+	–
Rhizomelic shortening of upper/lower limbs	7/12		Not typical		Mild	–	–
Pectus abnormalities	NR		54%		–	+	+
Low posterior hairline	NR		61%		–	+	+
Cryptorchidism	4/12		44%		–	+	–
Congenital heart defects	6/12		49%		–	Septal heart defect	Septal heart defect
Pulmonary stenosis			35%		–	NA	NA
Café au lait spots	1/12		10%		+	+	–
GH deficiency	3/11		In some cases		+	NA	NA
Hypothyroidism	4/11		NR		–	NA	NA

NR, not reported; NA, not assessed. [a]Santos-Simarro et al. [2021]. [b] Athota et al. [2020].

formed using an in-house pipeline based on the SeqMule pipeline (v1.2.6). Variant detection was carried out with the GATKLite variant caller, annotation and prioritization of variants were performed using KGGSeq (v1.0, 20/Jun./2018). Exclusion criteria for variant filtering were synonymous variants and variants with a minor allele frequency (MAF) higher than 0.75% in public databases (i.e., gnomAD, EXAC, 1000 GP, ESP).

Variant priorisation and evaluation of pathogenicity was based on different prediction tools (CADD, Polyphen, SIFT, Mutation Taster) and variant frequency in public databases. Variant confirmation in the patients and segregation analysis were performed by Sanger sequencing.

Growth percentiles and Z-scores were calculated using WHO reference data (https://www.cdc.gov/growthcharts/).

Results

WES in patients II-1 and II-7 revealed variants in 3 genes which have already been reported to be associated with growth retardation phenotypes.

In patient II-7, homozygosity for a 1-bp substitution in *CEP57* was detected, resulting in a premature stop codon NM_014679.4: c.973C>T, p.(Arg325*). The variant was neither listed in ClinVar and GnomAD nor reported in the literature and has been submitted to LOVD (variant ID 0000832117).

Segregation analysis confirmed heterozygosity in both parents, but patient II-1 did not carry the variant. The healthy sibs (II-5 and II-8) were heterozygous.

In patients I-1 and II-1, a heterozygous missense variant was identified in *PTPN11*. The variant NM_002834: c.317A>C, p.(Asp106Ala) has already been listed in dbSNP (rs397507517), in ClinVar and in the literature it is reported as "pathogenic" causing NS [Tartaglia et al., 2002; Hung et al., 2007]. In contrast, SIFT predicts variant as "tolerated" (score: 0.09, median: 3.51). Segregation analysis revealed heterozygosity in the father as well. Patient II-7 and the healthy siblings (II-5 and II-8) did not carry this variant.

Furthermore, compound heterozygosity for 2 missense variants in *POC1A* [NM_015426: c.784C>T, p.(Arg-262Trp) and NM_015,26: c.257G>A, p.(Arg86His)] was identified in the brothers. Both variants have already been reported in dbSNP (rs146976547, rs752711019) and in gnomAD with an allele frequency of 0.03 and 0.01%, respectively. The c.784C>T variant was listed in ClinVar as well and classified as "Variant of unknown significance".

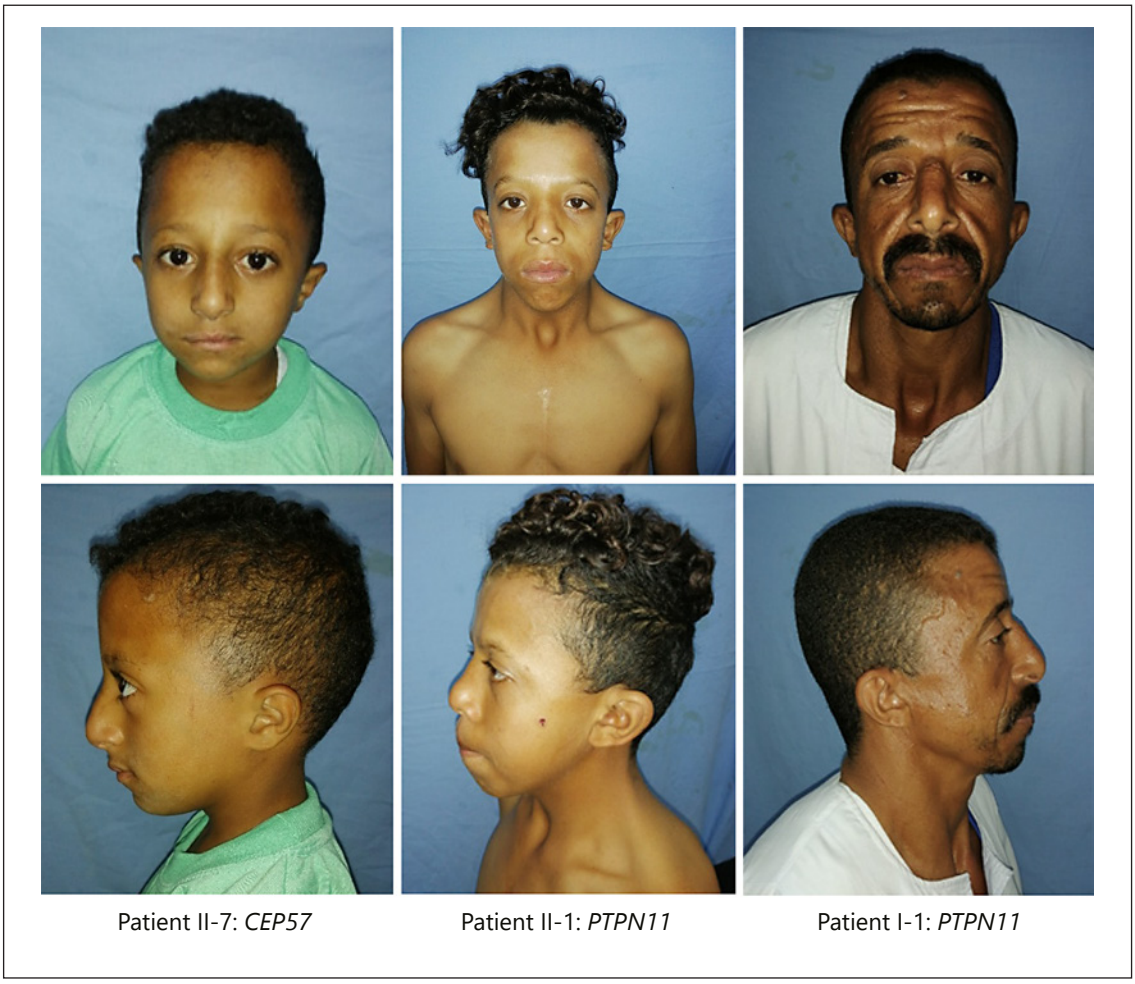

Fig. 1. Clinical presentation of patients II-7 (age 9 years), II-1(age 15 years), and I-1 (age 37 years).

By SIFT, both variants were classified as "deleterious". *POC1A* variants are associated with SOFT syndrome (OMIM 614813), resembling the phenotype of the patients from our family [Shaheen et al., 2012; Saida et al., 2019]. However, the variants were excluded to be disease-causing as the sister II-8 was compound heterozygous as well but did not exhibit the patients' features. Further putatively pathogenic variants in other genes associated with the clinical symptoms of the patients were not observed.

Discussion

Here, we report on a family with 2 different genetic disorders but overlapping growth retardation phenotypes (Table 1), constituting a challenge for the interpretation of WES data and illustrating the need for a careful anamnesis and molecular workup in affected and healthy family members.

By considering the clinical overlap between patients II-1 and II-7, a common cause for the small stature was assumed in the beginning, and WES revealed compound heterozygosity for 2 missense variants in *POC1A*, but the variants did no co-segregate with disease in the family and were therefore excluded.

Further data analysis showed no variants shared by the 2 brothers that could explain their phenotypes. However, 2 independent genetic causes for the short stature in the 2 brothers and their father could be identified, i.e., pathogenic variants in *CEP57* and *PTPN11* (Fig. 2). Detailed clinical analysis revealed a considerable overlap of the clinical features in both brothers II-1 and II-7 and their

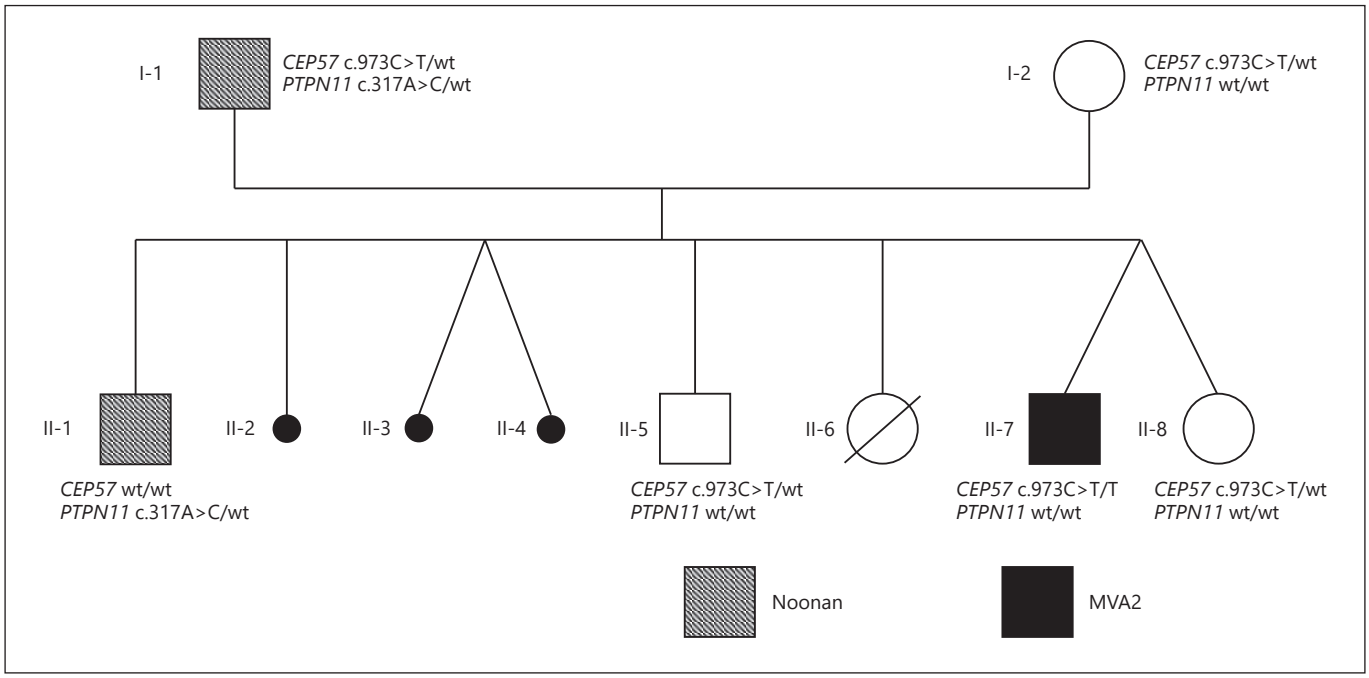

Fig. 2. Segregation of the variants in *PTPN11* and *CEP57* in the family with 2 genetic disorders.

father I-1. In addition to short stature, microcephaly with prominent forehead and low set ears were visible (Fig. 1), but clinical differences were recognizable as well; patient II-7 exhibited a more severe growth retardation phenotype than his brother and father. Hyperpigmentation, a high frontal hairline and a prominent nose were discriminating features for patient II-7. Unique features in patients II-1 and I-1 were septal heart defects, a webbed neck, and downslanting palpebral fissures.

The clinical phenotype of patient II-7 is consistent with *CEP57*-associated MVA2 (Table 1). All 12 patients from the literature exhibited a severe postnatal growth retardation, most of them had facial dysmorphisms including triangular face, prominent forehead, micrognathia, and small, low-set ears. While congenital heart defects and vascular malformations are relatively common in patient with *CEP57* [Santos-Simarro et al., 2021], patient II-7 did not exhibit anomalies of the heart. In mouse models, *CEP57* has been identified as a haploinsufficiency tumor suppressor [Aziz et al., 2018], but tumors have not yet been reported in MVA2 patients with *CEP57* variants. However, an increased tumor risk cannot be ruled out in *CEP57*-associated MVA2 due to the small number of cases [Dery et al., 2020; Santos-Simarro et al., 2021].

Up to now, only 4 different variants in *CEP57* have been reported in patients with MVA2 in the literature [Santos-Simarro et al., 2021]. The majority of patients with MVA2 (8 out of 12) presented a homozygous 11-bp insertion in exon 9 (NM_014679.4: c.915_925dup11). Six of them were of Moroccan origin, 1 of them of Mexican, and 1 of Caucasian origin [Snape et al., 2011; Pinson et al., 2014; De la Torre-Carcia et al., 2019; Dery et al., 2020; Pezzani et al., 2020; Santos-Simarro et al., 2021]. A compound heterozygosity of the variant c.915_925dup11 in combination with a 2-bp deletion (c.520_521delGA) was reported as well [Snape et al., 2011]. Additionally, a homozygous 1-bp deletion (c.679delA) and a 1-bp substitution (c.241C>T) have been described in 1 Pakistanian and 1 Caucasian patient [Snape et al., 2011; Brightman et al., 2018]. With c.973C>T, a fifth variant could now be identified in an Egyptian family. Most of the reported variants are nonsense variants resulting in truncated proteins, if expressed. The variant reported here can be assumed to be likely pathogenic according to ACMG-Guidelines [Richards et al., 2015], because it results in a premature stop codon and is rare in reference databases. In summary, our patient II-7 corroborates the assumption that *CEP57* variants are a molecular cause for MVA2.

Patients II-1 and I-1 presented a classical NS phenotype with growth retardation and posteriorly rotated, low set ears. However, overlapping phenotypes in the same family make the clinical diagnosis challenging. Many

small stature syndromes share clinical features with MVA2 and NS. As listed in Table 1, key diagnostic criteria of NS, e.g., specific facial dysmorphisms, cryptorchidism, and heart defects, also belong to the phenotypic spectrum of MVA2.

A major difference between NS and MVA2 is the response to growth hormone (GH) treatment. In patients with NS carrying *PTNP11* variants, height increases under treatment by up to 1.53 SD [Seok et al., 2020]. In contrast, MVA2 patients probably do not benefit from GH treatment. In fact, due to the function of *CEP57* and based on mouse models, a potentially increased tumor risk should be considered, and accordingly GH treatment has to be applied with caution in carriers of pathogenic *CEP57* variants [Santos-Simarro et al., 2021].

Coexistence of multiple molecular diagnoses in one person was detected in about 4.9% of investigated probands by WES, while the resulting diseases can be distinct or overlapping [Posey et al., 2017]. In this context, it can be assumed that different causes for similar phenotypes in one family are not at all uncommon, even if large studies on this are lacking.

In summary, we report a family with short stature and 2 different molecular syndromes with similar clinical phenotypes. Thus, when including multiple patients from the same family in a parallel WES approach, the possibility of independent molecular causes should be considered. As the family reported here shows, the knowledge on the different molecular causes underlying the features of the affected family members is needed for personalised therapeutic managements and can avoid unnecessary burden and even contraindicated therapies.

Acknowledgement

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Statement of Ethics

The study was approved by the ethical committee of the Medical Faculty, RWTH Aachen university (EK303-18). Written informed consent was obtained from the family of the patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare not conflict of interest.

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Author Contributions

C.H., D.D., and R.M. conducted the laboratory and bioinformatics work. C.H. prepared the work. A.K.A. contacted the family, summarized the clinical data, and approved the clinical diagnosis. C.H., R.M., A.K.A., and T.E. prepared the paper; all authors approved the final version. T.E. supervised the study.

Data Availability Statement

Not applicable.

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