


# Rare NF1 microdeletion syndrome in an Omani patient

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## Key Clinical Message

Neurofibromatosis-1 phenotype combined with webbed neck and short stature in a young Omani patient was revealed to be due to a de novo germ-line heterozygous 1.7 Mb microdeletion at 17q11.2. This led to the diagnosis of NF1 microdeletion syndrome.

## KEY WORDS

comparative genomic hybridization, microdeletion, neurofibromatosis type 1, noonan syndrome

## 1 | SHORT REPORT

We present a first case report from Oman of a 20-month-old male child presenting with a neurofibromatosis-1 phenotype combined with webbed neck and short stature. Comprehensive molecular testing revealed a de novo germ-line heterozygous 1.7 Mb microdeletion at 17q11.2, which led to the diagnosis of NF1 microdeletion syndrome.

We present a case of a 20-month-old male child, born prematurely (33 weeks) with IUGR (intrauterine growth restriction) after elective cesarean section to a mother who had a history of a previous abortion and one healthy offspring. The index patient presented here was the product of a non-consanguineous marriage and has no family history of dysmorphic or disability syndromes. After birth, the patient was admitted to the neonatal intensive unit for 25 days. He initially presented with abnormal facial features and developmental delay and was referred to our center for further evaluation and management at 2 years of age. Along with delayed development, the patient mainly presented with the clinical features in Table 1, which were highly suggestive of Neurofibromatosis Type 1 (NF1) associated with mutations in the NF1 gene.

The patient also exhibited short stature, webbed neck, and cardiac defect at birth, (which resolved with time)

all symptoms which are commonly seen in Noonan syndrome (NS) patients. This led to a preliminary diagnosis of Neurofibromatosis-Noonan syndrome (NFNS) in this patient (Figure 1).

NFNS is typically described as a rare autosomal dominant disorder with combined clinical features of NF1 and Noonan syndrome (NS).<sup>1</sup> To confirm this diagnosis, the patient was referred for molecular genetic testing to the laboratory at our center where the patient's blood was collected after informed parental consent. DNA was extracted from the patient's blood and processed for next-generation sequencing (NGS) using the Ion AmpliSeq Comprehensive Cancer panel (CCP) on the Ion S5 from Ion Torrent (ThermoFisher Scientific) to probe for mutations in the NF1 gene and three of the most significant genes causing NS, namely PTPN11, SOS1, and KRAS. Since the CCP is also validated in our laboratory for use as a preliminary screen for copy number variants above 200 kb, we were able to detect an apparent 279 kb deletion at the 17q11.2 (hg19) locus using NGS. This 279 kb deleted region indicated a single copy loss for five non-consecutive genes present within the 17q11.2 locus, including the NF1 gene. This signified the presence of a microdeletion event at this locus. However, NGS cannot reliably provide information regarding the full extent of microdeletions or their breakpoints because NGS results only

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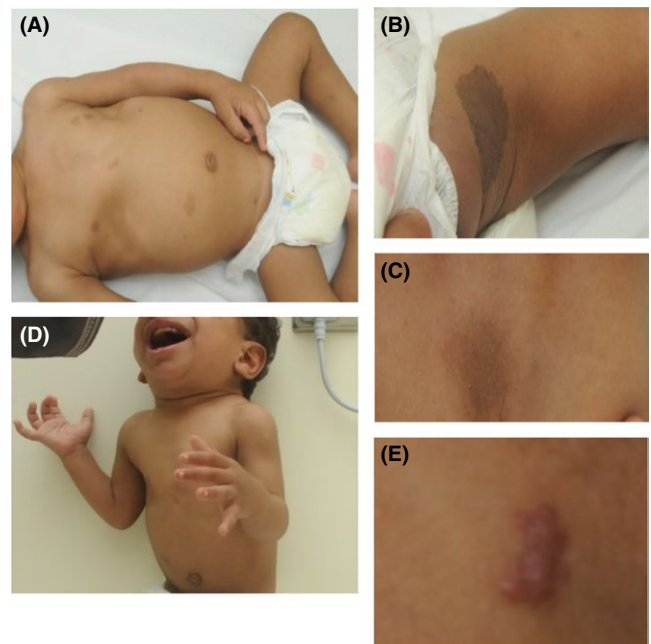
**TABLE 1** Abnormalities observed in the index patient

<b>NF1 phenotype</b>	Widely spaced nipples (internipple distance = 13.9 cm; >97 percentile at age 3 y)
Multiple café au lait macules	
<b>Pectus deformity</b>	<b>Ophthalmology investigations</b>
Nevus anemicus	Two lisch nodules in each eye
Large hands and feet	Retinal pigmentary epithelial changes close to optical disk in left eye
Single juvenile xanthogranuloma	
<b>Ptosis</b>	<b>Other investigations</b>
Thick skin	Chromosomal karyotyping: 46, XY
High-arched palate	Echocardiogram: Normal at last evaluation
Low set ears	Whole Spin X-ray: Inferior peaking of upper lumbar vertebrae
Broad forehead	CT Brain: Normal
Down-slanting palpebral fissures	
Depressed nasal bridge	<b>NS-like phenotype</b>
Kyphosis	Webbed neck
Hypertelorism	Short stature
	Cardiac anomaly at birth (resolved with time)

reflect the genes probed by the specific panel, which are likely less than the actual number of genes or regions deleted.

In view of establishing the diagnosis of neurofibromatosis, we used the Multiplex ligation probe amplification (MLPA) kits from MRC Holland (P081-D1 and P082-C2) to confirm the complete heterozygous NF1 gene deletion (exons 1-58) in the index patient. Since the index patient presented with webbed neck and relatively severe developmental delay, features rarely seen in NF1 patients, we further sought to delineate the microdeletion breakpoint regions and characterize the genes in the deleted locus. The patient DNA was processed for comparative genomic hybridization (CGH) array on the Affymetrix platform using the CytoScan HD kit, and data analysis was carried out using the CHAS software (v.3.1.0.15). CGH array analysis revealed a heterozygous microdeletion of almost 1.7 Mb in the distal part of chromosome 17 (17q11.2) in the index patient. This 1.7 Mb microdeletion region {arr[hg19]17q11.2(28,838,381-30,533,034) x1} actually included 22 genes, of which 11 were OMIM genes [CRLF3 (614853), ATAD5 (609534), ADAP2 (608635), RNF135 (611358), NF1 (613113), OMG (164345), EVI2B (158381), EVI2A (158380), RAB11FIP4 (611999), MIR193A (614733), SUZ12 (606245)]. Out of these 11 OMIM genes, only two genes, RNF135 and NF1 were associated with disease phenotypes. A previous study on a patient with haploinsufficiency of the RNF135 gene due to a microdeletion encompassing RNF135 and another four genes, but excluding NF1, suggested that haploinsufficiency of RNF135 may contribute to the overgrowth, facial dysmorphism, learning

disabilities and other congenital anomalies exhibited by patients with NF1 microdeletions.<sup>2</sup> However, despite the absence of one RNF135 gene copy, our patient did not show any overgrowth symptoms, although facial dysmorphism was noted. On the contrary, the patient continued to exhibit short stature till last clinical visit 8 months ago.



**FIGURE 1** NFNS presentation in the index patient (A) café au lait spots, pectus deformity, and widely spaced nipples (B) large café au lait spot on the inner thigh (C) nevus anemicus (D) webbed neck, large feet, and hands (E) Juvenile xanthogranuloma

Given the preliminary diagnosis of NFNS, we sought to rule out Noonan syndrome by analyzing all the associated genes (A2ML1, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SPRED1) using a custom NGS panel. However, no pathogenic or candidate variants were detected in these genes. Hence, our comprehensive testing resulted in revising the diagnosis from NFNS to NF1 microdeletion syndrome in our patient; the first such case to be reported in Oman. Although a 1.7 Mb microdeletion associated with the NF1 gene was previously reported elsewhere using the FISH technique in 1999,<sup>3</sup> it was present in mosaic form. Moreover, the range of the region and the genes deleted were not well defined, likely due to the lack of advanced CGH array technology at the time.

It is not surprising that patients with mutations in the NF1 gene can also present with features overlapping with those seen in NS patients, considering that both the NF1 gene and the NS genes express proteins which are integral components of the RAS-MAPK developmental pathways during embryogenesis.<sup>4</sup> Also, the complete loss of one of the alleles of the NF1 gene is the probable cause of the relatively more severe and earlier presentation of cognitive abnormalities and dysmorphism in our patient, a phenomenon also observed in previous reports of NF1 microdeletions.<sup>5-9</sup>

Although SNP analysis using array CGH indicated that the microdeleted allele was maternal in origin, no genomic abnormality was detected in either parent. Hence, we concluded that this 1.7 Mb microdeletion within the 17q11.2 region probably occurred as a de novo event. The clinical management protocol adopted for this patient was based on the international guidelines for NF1 patients, which primarily focus on the evaluation and treatment of complications.<sup>10,11</sup> We referred the patient to appropriate specialists as part of a management plan to include regular clinical evaluation, assessment of developmental milestones and annual ophthalmologic examination to enable early or preventive interventions. A periodic follow-up using magnetic resonance imaging (MRI) for potential intracranial tumors and other internal tumors was also implemented.

## CONFLICT OF INTEREST

The authors of this manuscript have no conflict of interests to declare.

## AUTHOR CONTRIBUTION

MA: conducted clinical sampling, patient counseling, and manuscript review. NH: carried out molecular genetic analyses and wrote the manuscript. AAY, HAM, AE, AAA:

carried out cytogenetic and molecular cytogenetic analyses. SAH: supervised cytogenetic work. LH: carried out molecular genetic work-up. WM: carried out manuscript review.

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