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Case Report

Rupture of Abdominal Aortic Aneurysm and Renal Failure in an Adult Patient with NF1 Micro duplication

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Abstract

Neurofibromatosis Type 1 (NF1) is an autosomal dominant disorder affecting 1/ 3000 individuals and caused by Single Nucleotide Variants (SNVs), deletions and duplications affecting the *NF1* gene. Vascular lesions of medium and large size arteries and veins are a well recognized, albeit rare, manifestation of NF1. We report an adult patient retrospectively diagnosed (clinically and molecularly) with NF1 after surgery for a ruptured abdominal aortic aneurysm and renal failure. The 37 year old female patient was admitted for emergency surgery due to a ruptured abdominal aortic aneurysm, renovascular hypertension and renal failure. The other clinical manifestations of NF1 included multiple café-au-lait macules, axillary fleckling, multiple cutaneous neurofibromas, and an external vaginal plexiform neurofibroma. Genomic DNA from peripheral blood was analyzed by Next Generation Sequencing (NGS) and Chromosomal Microarray Analysis (CMA). NGS did not reveal a pathological SNV for the *NF1* gene but the CMA revealed a novel duplication covering exons 19-27. To our knowledge, very few cases with partial *NF1* gene duplications have been reported so far. In addition, our patient presented also an abdominal aortic aneurysm. The rare presentation of cases with NF1 vasculopathy could be due to an under-appreciation of its recurrence.

Introduction

Neurofibromatosis Type 1 (NF1, OMIM# 162200) is a dominant disorder with a worldwide birth incidence of approximately 1 in 2000 to 1 in 3,000 individuals. The main clinical symptoms include café-au-lait macules (CALM), skin fold freckling, cutaneous neurofibromas, plexiform neurofibromas, optic gliomas and Lisch nodules of the iris. Disease penetrance is 100% and patients present mutational, allelic or phenotypic heterogeneity [1].

The disease is caused by SNVs or deletions/duplications of the *NF1* gene, located on chromosome 17q11.2. The *NF1* gene consists of 57 constitutive exons and three alternative spliced exons and it is expressed in almost all tissues. Large 17q11.2 deletions are present at about 5 to 10% of patients and are related to a more severe phenotype [2]. The *NF1* gene is located at a genomic region that contains 3 low copy repeats which predispose this region to rearrangements by nonallelic homologous recombination. This process results to NF1 micro deletion syndrome (OMIM# 613675). Intragenic duplications or deletions of one or more exons account for <2% of molecular aberrations causing NF1 [3].

NF1 microduplications have been reported in the literature and have been associated with unusual phenotypes, such as facial dysmorphisms, early onset of baldness and dental enamel hypoplasia, variable intellectual disability, developmental delay, lymphoproliferative malignancies etc. CALM and neurofibromas have been reported in only 3 cases with NF1 microduplications [4,5].

Vasculopathy is a rare manifestation of NF1 with an unknown frequency. Most of the patients are asymptomatic and the impairment may vary from vascular stenosis to aneurysm, rupture etc. Renal arteries are affected mostly in NF1-associated vasculopathy [6]. In the present report we describe a case of NF1 vasculopathy with a ruptured abdominal aortic aneurysm and renal failure.

Case presentation

A 37-year-old female patient was admitted for emergency surgery due to ruptured abdominal aortic aneurysm, renovascular hypertension and renal failure. Signs of NF1 became evident upon patient physical examination. The clinical characteristics included multiple CALMs ≥5 mm, axillary fleckling, multiple cutaneous neurofibromas, macrocephaly and an external vaginal plexiform neurofibroma.

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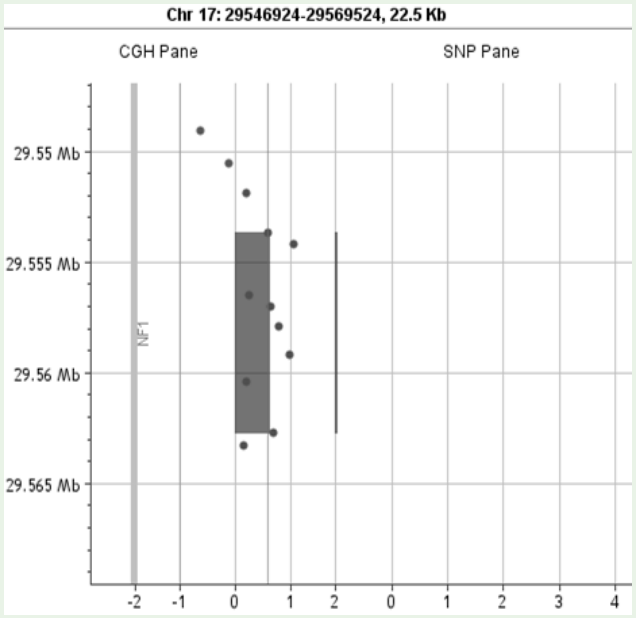

Figure 1: CMA presentation of *NF1* gene duplication.

Genomic DNA was extracted from peripheral blood lymphocytes using the QIAamp DNA Blood Mini Kit (Qiagen GmBh, Hilden, Germany) and was analyzed by Next Generation Sequencing (NGS) with a custom panel (QIAseq, Qiagen GmBh, Hilden, Germany) that covers 100% of the coding exons and the intron-exon boundaries. The protocol was designed according to previous study [7]. Additionally, Chromosomal Microarray Analysis (CMA) was done using the high resolution 2x400K G3 CGH+SNP microarray platform (G4842A, Design ID 028081, Agilent Technologies and Santa Clara, CA, USA).

NGS did not reveal a pathological SNV for the *NF1* gene but the CMA revealed a novel duplication at 17q11.2 spanning about 9 Kb of genomic DNA. The duplication contains exons 19-27 of the *NF1* gene [17q11.2 (29553704-29562744) x3] (Figure 1). No other family members were available for testing.

Discussion

The present case is a good example of reverse genetics. The 37 year old female patient presented spontaneously ruptured abdominal aortic aneurysm of unknown cause and only after molecular diagnosis and further medical examination, she was characterized as an NF1 patient with all the characteristic signs of the disease (neurofibromas, wide distribution of CALM on face, arms and torso and macrocephaly). The patient was counseled for regular clinical follow-up regarding other NF1 symptoms (Lisch nodules, optic gliomas or specific tumors).

Patients with NF1 microduplications, in contrast to those with NF1 microdeletions, present with atypical clinical manifestations, such as intellectual disability, developmental delay and facial dysmorphisms. The reported microduplications affect the entire NF1 gene, as well as 14 neighboring genes [8]. In the present case study, we report a novel intragenic duplication of only 9 Kb of genomic DNA in a patient with typical signs of the disease. To our knowledge, very few cases with partial NF1 gene duplications have been reported so far [9,10]. More patients with NF1 microduplications are required in order to attempt possible genotype- phenotype correlation.

In addition, our patient presented also an abdominal aortic aneurysm. The rare presentation of cases with NF1 vasculopathy (abdominal aortic coarctation, internal carotid artery aneurisms and cervical vertebral arterio-venous fistulae) could be due to an under-appreciation of its recurrence [6].

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