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Case Report

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NF1 gene mutations are the major molecular event in neurofibromatosis-noonan syndrome

Abstract

Neurofibromatosis–Noonan syndrome is a rare autosomal dominant disorder which combines neurofibromatosis type 1 (NF1) features with Noonan syndrome. Noonan syndrome (NS) and the clinically overlapping disorders and Neurofibromatosis-Noonan syndrome (NFNS) share the some common clinical features. It is now known that all these disorders are caused by mutations in components of the RAS-MAPK signaling pathway which is important in tumorigenesis. NF1 gene mutations are reported in the majority of these patients. There are some data in the literature about the NF1 mutant allele which can lead to manifestations of Noonan syndrome. We have studied four NFNS cases which all fit the NFNS criteria. We evaluated these patients one with Watson syndrome (WS) and the other one with Rhabdomyosarcoma. Although WS and NFNS were described as distinct disorders, detailed clinical examination of these families revealed that not only pulmonic stenosis, borderline intelligence, and multiple cafe´-au-lait spots, but also multiple Lisch nodules, neurofibromas in one third of patients, and short stature were present. The only distinction between WS and NFNS would be that NFNS patients show a more classical phenotype of both NS and NF, whereas WS patients show only a mild expression of NF. Recently, there is increasing evidence for WS and NFNS being allelic to NF1 in the majority of patients. We analyzed 4 NFNS patients by PCR based techniques. Genomic DNA was extracted from peripheral blood samples. PCR was performed with intronic primers for all exons of the NF1. DNA samples were sequenced to detect variations in each exon. This study supports that the major gene causing NFNS is NF1. Therefore inclusion of NF1 in the genetic screening of patients with clinically suspected NS, preferentially when café-au-lait spots are present. As a result, the present study provides the molecular evidence of the role of NF1 mutations in NFNS.

Keywords: neurofibromatosis type 1,noonan syndrome;neurofibromatosis - noonan syndrome, nf1 gene mutations

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Abbreviations: NF1, neurofibromatosis type 1; NS, noonan syndrome; NFNS, neurofibromatosis-noonan syndrome; WS, watson syndrome; LOH, loss of heterozygosity; PCR, polymerase chain reaction; CLS, café-au-lait spots; AF, axillary freckling; IF, inguinal freckling; LN, lisch nodules; SD, skeletal dysplasia; RMS, rhabdomyosarcoma

Introduction

The Neurofibromatosis type 1 disease (NF1) (OMIM:162200), which is known also as von Recklinghausen's Disease, is an autosomal dominant disorder with an estimated frequency of 1 in 2500 to 3000 live births.[1] The gene of neurofibromatosis type 1 is located at chromosome 17q11.2.[2] Approximately 50% of all affected individuals carry *de novo* mutations.[3,4] Typical appearances are café-au lait spots, peripheral neurofibromas, Lisch nodules, axillary and inguinal freckling,, malignant peripheral nerve sheath tumors (MPNST) (Neurofibromas as a benign form and Neurofibrosarcomas as a malignant forms) and other malignancies such as intracranial astrocytomas, gastrointestinal stromal tumors, pheochromocytomas, and juvenile monocytic leukemia.[2,5] Endocrine symptoms, neurological and ophthalmological problems are the other manifestations that appear less frequently.[6]

Noonan's syndrome (NS) (OMIM: 605275) is also an autosomal dominant disorder with massive heterogeneity in clinical and genetic features same as NF1. The incidence of NS is 1 in 1000 to 2500 live births.[7] The clinical feature of NS is short stature, congenital heart defects, unusual pectus deformity, and typical facial features, such as hypertelorism, ptosis, downslanting palpebral fissures, low-set posteriorly rotated ears, and a broad forehead. Additional associated features include neonatal failure to thrive, bleeding abnormalities, mild intellectual disability, multiple skeletal defects, and various skin manifestations, for example, cafe´-au-lait spots[2,8,9] with both hematopoietic malignancies and malignant solid Tumors.[10] Nine genes involved in the RAS-MAPK pathway are known to be associated with 70-85% of patients with NS or NS-like conditions. These genes are PTPN11 (responsible gene for 50% of patients), SOS1, KRAS, NRAS, BRAF, RAF1, MAP2K1, CBL, and SHOC2.[11]

A atypical clinical association of these two disorders, named Neurofibromatosis-Noonan syndrome (NFNS) MIM 601321 is first noted in 1985 by Allanson and colleagues.[12] They described subjects with features of both NF1 and NS [13]. Though it has been long speculated for many years that whether NFNS is a different form of either NF1 or NS or they are distinct disorders,[14] approximately the 13% of patients with NF1 display the phenotypic features of NS.[15] This phenotype in such cases is most probably produced by genes that are very close to the NF1 locus or by variable expression of NF1 gene.[16] In this study the aim is to support that NF1 gene mutations are the major causing NFNS.

Case Presentation

The clinical and genetic analyses were performed according to the guidelines in the Declaration of Helsinki and approved by the ethical committee of Hacettepe University, Turkey. This study included four individuals from unrelated families, presenting clinical features of both NF1 and NS. To diagnose the NF1, the NIH-consensus statement

was used,[6] and to diagnose NS a checklist of phenotypic features was used.[17]

Patients

This study included four individuals from unrelated families, presenting features of both NF1 and NS.

Case 1: An 11-years-old girl with familial history of NF1. She presented NS symptoms together with café-au-lait spots distributed throughout the body together with axillary frecklings and Lisch nodules.

Case 2: A 16-years-old boy with familial history of NF1. The Physical examinations and ultrasonography results showed the presence of Noonan and Watson syndromes (pulmonary valvular stenosis, relative macrocephaly, and short stature) together with café-au-lait spots and bone dysplasia.

Case 3: A 6-years-old boy without familial history. The presence of café-au-lait spots with NF1 gene mutation and symptoms of NS was detected.

Case 4: A 12-month-old boy without familial history with the complaints of difficulty urinating and abdominal distention. He had café-au-lait spots throughout the body together with inguinal freckling. The patient's facial appearance and the clinical features was distinct for NS.[18]

DNA analysis

Genomic DNA was extracted from peripheral blood leukocytes from affected and healthy individuals according to standard procedures. Genomic DNA samples were PCR amplified with intronic primers for all exons and sequenced in both forward and reverse direction for all exons and flanking intron sequences of NF1. NF1 mutations were detected in 3 of patients with Noonan syndrome (Table 1).

Table 1 Summary of Noonan patients with and without mutations in NF1 gene

No	Pt. No		Exon	Nucleotide Change	Mutation	Clinical Symptoms
1	45	familial	-	not detected	-	CLS, AF, LN, Noonan
2	124	familial	16	c2851-16T>C	nonsense	CLS, SD, Watson, Noonan
3	329	sporadic	26	c.4397C>T	Missense	CLS, Noonan
4	385	sporadic	Whole gene	Large Deletion	Deletions	CLS, AF, IF, Rhabdomyosarcoma, Noonan

CLS: Café-au-lait Spots ; AL: Axillary Freckling; IF: Inguinal Freckling; LN: Lisch Nodules; SD: Skeletal Dysplasia

Discussion

In the literature it has mentioned that several gene mutations are associated with NS. However, there have been several reports supporting the existence of NF1 gene mutations in the NFNS cases. In the first report, 3-bp deletion was found in exon 17 in a two generation family with NFNS.[19] In another case, Baralle et al.,[19] found a 2-bp insertion in exon 23.2 and a 3-bp deletion in exon 25 in NFNS patients. Bahuau et al.,[2] also reported on a three-generation NF-NS family who has a nonsense mutation in exon 16. Moreover, Yimenicioglu et al.,[20] presented another case report with a point mutation c.7549C>T in exon 51 in NF1 gene for the typical phenotype of both NFNS.

Although NF1 gene mutations have been reported in NF-NS patients, there is still no genotype-phenotype correlation. The NFNS phenotype is heterogeneous at both the clinical and the molecular level. Several different causes may be involved in simultaneous occurrence of NF1 and NS. In our study we also detected NF1 gene mutations in three out of four NFNS cases which support that NF1 gene mutations seems like the major cause in NFNS cases. Therefore inclusion of NF1 in the genetic screening of patients with clinically suspected NS are important, preferentially when cafe´-au-lait spots are present. To confirm these associations and to give a better genetic counseling for these patients, further studies are required.

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Conflicts of interest

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