

Noonan syndrome and systemic lupus erythematosus in a patient with a novel KRAS mutation

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ABSTRACT

Noonan syndrome is characterised by distinct facial stigmata, short stature and congenital cardiopathy. It has a high genetic heterogeneity and mutations in six different genes can be involved. We report a patient with Noonan syndrome and a novel KRAS mutation who presents systemic lupus erythematosus.

Case report

Noonan syndrome (NS) is mainly characterised by short stature, distinct facial features and congenital cardiopathy (1). Facial features include broad forehead, hypertelorism, down-slanted palpebral fissures, high palate, low set ears and ptosis of the eyelids. PTPN11, KRAS, SOS1, RAF1, SHOC2 and NRAS are the responsible genes and belong to the RAS-MAPK pathway (1-3).

The diagnosis of NS in our 3-year-old female patient was based on clinical criteria (4). Facial characteristics (Fig. 1A), short stature, pectus excavatum and psychomotor retardation were indicative of NS. Karyotype was normal and DNA analysis revealed a novel missense mutation in the KRAS gene (c77A>T, pAsn26Ile) which has not been described in the literature before (Fig. 1B). Mutation analysis in both patients was negative indicating that this is a de novo mutation and not a polymorphism

At the age of 18 years, the patient presented with a papillary rash on the lower limbs and peripheral nonerosive arthritis. Additional clinical symptoms were fever, headaches and fatigue. Haematological laboratory findings were anaemia (Hct 19.9%), lymphopenia (1125/μl) and thrombocytopenia (6000/μl). Creatinine levels were normal and urine analysis demonstrated microhaematuria (8-10 RBCs/HPF). Inflammatory parameters were normal (CRP 3.2 mg/l, C3 0.99 gr/l, C4 0.175 gr/l) except positive IgG (18.7 gr/l). Infections were excluded. Coagulation tests were normal and direct Coombs was positive. The initial clinical scenario led to the diagnosis of thrombotic thrombocytopenic purpura. However, rheumatological assessment that was performed in an outpatient basis revealed antinuclear antibody (>1:40), high anti-DNA antibody (ELISA) (100IU/ml) and positive IgM anti cardiolipin (22.7 MPLU/ml, normal range <12.5). The previous clinical and laboratory findings were consistent with SLE diagnosis (5). High doses of corticosteroids (prednisone 100 mg/d) and fresh frozen plasma were administered and the patient was treated further with low dose of corticosteroids being in a remission state.

Hypertrophic cardiomyopathy was found when Noonan clinical diagnosis was set. Echocardiographic findings

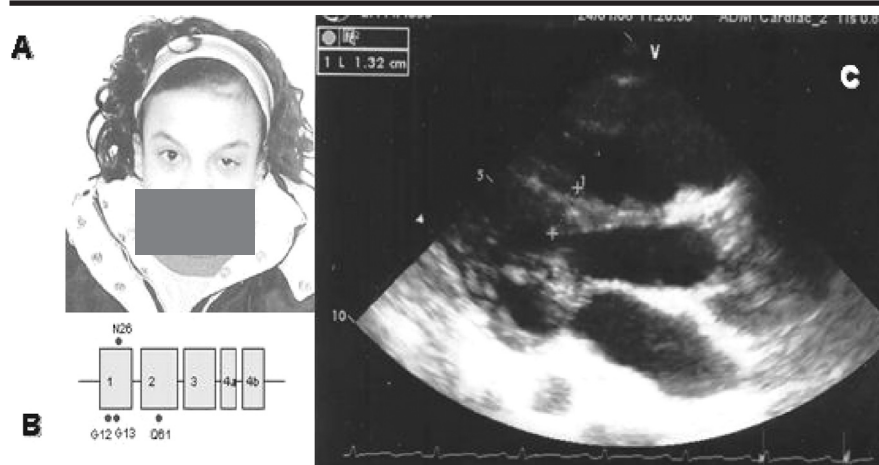


Fig. 1 A. Typical facial characteristics of Noonan syndrome.

B. Ideogram of the KRAS mutation. The position of our mutation (top) and the location of the most frequent mutated residues in cancer on KRAS (bottom) are depicted.

C. Long axis view by transthoracic ultrasonography. Asymmetric hypertrophy of the interventricular septum is illustrated and measured at 13 mm at the age of 18 years.

Competing interests: none declared.

remain the same till the age of 18 (Fig. 1C) and the patient has been on β -blocker therapy.

KRAS mutations are present in around 2% of Noonan patients (6). Autoimmune disorders are a rare manifestation of NS. Co-existence of NS and SLE (five cases) has been reported (7, 8). According to linkage analysis the responsible region for development of SLE was located between 12q24.1 and 12q24.3 which encompasses the most common affected gene (PTPN11) in NS (9). This observation implies a potential correlation between NS and SLE. Additionally, NRAS mutation was described in a patient with autoimmune lymphoproliferative syndrome (ALPS) (10).

Our patient has a novel mutation in the KRAS gene and no other cases with NS, SLE and a KRAS mutation are reported so far. The co existence of NS and SLE in a patient with a KRAS mutation denotes the complexity of the genetic contribution to SLE.

Hypertrophic cardiomyopathy is more frequent in SOS1, KRAS and RAF1 patients, whereas PTPN11 patients most frequently have pulmonary valvular stenosis (4).

It is clear that more research is necessary to clarify the crucial mechanisms – if they exist – that associate Noonan syndrome and RAS-MAPK activation with SLE. However, it is apparent that Noonan syndrome patients need constant follow-up and demand high clinical awareness in order to achieve prompt treatment of any clinical comorbidities.

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