



## Variable Phenotypic Expression Including Late Presentation of Hypertrophic Cardiomyopathy in LEOPARD Syndrome with P.Q510E Mutation in PTPN11 Gene

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### Abstract

LEOPARD syndrome is a complex dysmorphogenetic disorder of variable penetrance and expressivity. Mutations in the PTPN11 gene are frequently reported in patients with Noonan syndrome (NS) and LEOPARD syndrome (LS). Q510E mutation in PTPN11 has always been associated with lethal or rapidly progressive hypertrophic cardiomyopathy both in NS and LS patients. Besides, deafness is also frequently present in these patients, but reproductive fitness is questioned.

We herein describe a case of LEOPARD syndrome from Bangladesh with Q510E mutation in the PTPN11 gene. Our patient almost fulfilled the entire acronym of LEOPARD with very late presentation of hypertrophic cardiomyopathy at the age of 36 yrs. Interestingly patient has intact hearing and normal reproductive capacity, biologically fathered two children.

### Keywords

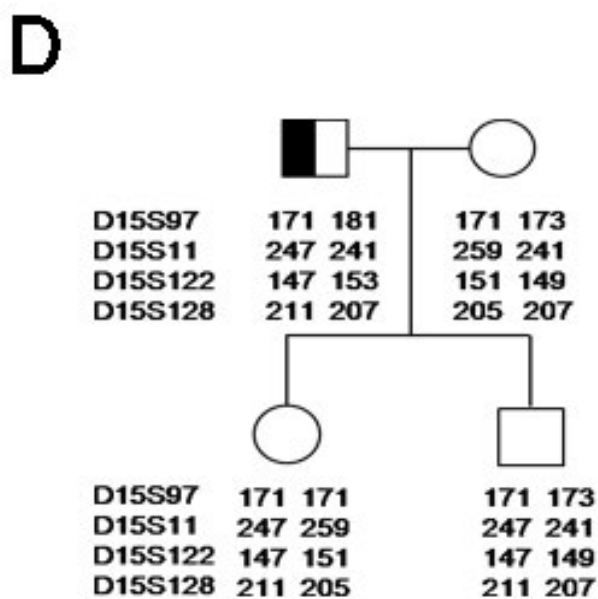
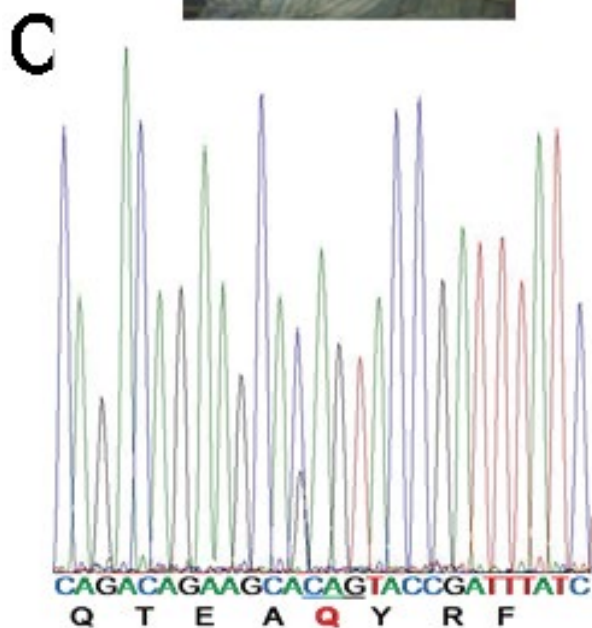
LEOPARD syndrome, Noonan syndrome with multiple lentigines (NSML), PTPN11 gene, Q510E mutation, Hypertrophic cardiomyopathy, Fertility, Bangladesh

### Introduction

LEOPARD syndrome (LS) is a rare autosomal dominant cardiocutaneous syndrome characterized by variable penetrance and expressivity. It is an acronym for the Lentigines, ECG abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retarded growth and Deafness, was introduced by Gorlin in 1969 [1]. The name LEOPARD syndrome could be felt to be stigmatizing by

patients and their families, therefore, currently efforts are underway to change it to Noonan syndrome with multiple lentigines (NSML). Advances in molecular genetics research have led this disease to be a part of new group of genetic syndromes named as the RAS-MAPK pathway disorders or 'RASopathies' that involve different steps of signaling cascade [2]. Clinical diagnosis of LS is based on the most common presentation of lentigines and 2 other symptoms. In cases without lentigines, 3 symptoms and at least one affected first degree relative fulfill the diagnostic criteria [3]. Although pulmonary valve stenosis with or without dysplasia is a part of the acronym but current data consistently show a low figure for this defect [4]. Conversely, hypertrophic cardiomyopathy (HCM) though not included in the acronym is the most frequent cardiac anomaly detected in up to 80% of the subjects and is considered to be the only life threatening problem [5]. Molecular studies have proven that LEOPARD syndrome and Noonan syndrome are allelic disorders caused by different missense mutations in PTPN11, a gene encoding the protein tyrosine phosphatase SHP-2 located at band 12q24.1 [6]. But a pathogenic mutation causal to the disease could be found in any of the three genes: PTPN11, RAF1, and BRAF. In ~85% of the cases a heterozygous missense mutation is detected in exons 7, 12 or 13 of the PTPN11 gene [7], affecting tyrosine phosphatase, non-receptor type that implicates signal pathway between cell membrane and the nucleus [8]. LS greatly overlaps in clinical features with NS, an allelic disorder caused by different missense mutations in PTPN11 and specific mutations of the PTPN11 gene are associated with 50% of the NS cases [7,8].

Presence of multiple lentigines, *café-au-lait* spots (CLS) and



**Figure 1A:** Patient of LEOPARD syndrome.

**Figure 1B:** Echocardiogram showing asymmetric septal hypertrophy.

**Figure 1C:** Electropherogram showing Q510E mutation in proband.

**Figure 1D:** Paternity test confirms intact fertility of proband.

familial predisposition are commonly reported in LS and mostly transmitted from mothers, possibly related to the reduced male fertility. In sporadic cases, a *de novo* mutation is usually found and the recurrence risk in siblings is minimal [7]. Generally long-term prognosis of LS patients is favorable and most adults do not require special medical care except cardiac cases that require periodic assessment. Medical treatment with beta-blocker and calcium channel blocker is indicated when obstructive variety of HCM is present. Surgical myomectomy and an Implantable Cardioverter Defibrillator (ICD) implantation are considered in severely symptomatic patients. We present a case of LS involving PTPN11 gene mutation that uniquely presented with late HCM, absence of deafness and intact paternity and to the best of our knowledge it is the first of its kind reported from this locality.

### Case Report

A 36 year-old day laborer was admitted in the Cardiology unit of Rajshahi Medical College Hospital (RMCH), Bangladesh in April 2014 with complains of chest discomfort, exertional fatigue, shortness of breath and palpitation. Admission ECG showed extreme left axis deviation, prolonged P-R interval and non progression of R wave in V1 to V6. Initially he was thought to be a case of acute coronary

syndrome and treated accordingly. But careful examination revealed striking distribution of multiple lentiginos diffusely present all over the body including palms and soles sparing the mucous membranes. There were four cafe-au-lait spots in the left lateral aspect of the chest. Anthropometric measurement showed intercanthal distance 35 mm and interpupillary distance 65 mm suggesting the presence of ocular hypertelorism. His eye lids were swollen with congested conjunctivae and some degree of photosensitivity was present. Patient had mild prognathism and thick lips (Figure 1A). He had genital abnormality with undescended left testis located in deep inguinal ring and normally positioned urethral orifice; skin was soft in texture with hyperelasticity and hypermobile joints. There was mild slurring in speech and low intellect noted during close communication. His height was 158 cm, weight 48 kg with below average built, pulse 60/min and blood pressure 90/60 mm Hg. He was not anemic and there was no palpable lymph node. His visual acuity and color vision were normal with normal external appearance of ear and hearing ability as revealed in audiometry. He had pectus excavatum and a systolic murmur was present at base and left sternal border (Figure 1A).

Echocardiogram revealed grossly hypertrophied septum without any LVOT obstruction suggesting asymmetric septal hypertrophy (Figure 1B). Valve functions including pulmonary valve and LV

functions were normal. His chest x-ray, complete blood count with peripheral blood film, USG of whole abdomen and rest of the investigations were all normal. Patient was nonsmoker, normotensive, nondiabetic and there was no positive family history of such cardiac disease or multiple lentigenosis. His parents were nonconsanguineous with remaining children are healthy. Patient was married with two normal children. Compilation of presenting signs eventually fulfilled the entire acronym of LS except deafness and pulmonary stenosis.

Genetic analysis was done to confirm the clinical diagnosis and to exclude other cardiocutaneous syndromes especially Noonan's syndrome. It revealed a previously described [9,10] missense mutation (Q510E) in exon 13 of PTPN11 gene (Figure 1C). His wife and two children were screened and found negative for the mutation. Paternity test was positive for the children pointing to the patient's intact fertility (Figure 1D). During hospital stay; he was treated with beta blocker and found reasonably well. Discharge advices included avoidance of heavy exertion and to continue the drug. During one year follow-up, he has been doing reasonably well except occasional exertional fatigue.

## Discussion

Molecular identification of the Q510E mutation in PTPN11 gene confirms our patient as a case of LS though there was significant difference in the presentations of LS. Interestingly we noted some unique features in our patient alike most of the cases cited in the literature. Firstly, there was very late presentation of hypertrophic cardiomyopathy at the age of 36 yrs. without any lethal event. Usually Q510E mutation has been implicated in lethal progressive hypertrophic cardiomyopathy described exclusively in neonates and infants [10]. Secondly, there was no deafness in our case but in most of the cases of LS described so far, loss of hearing was among the major presenting clinical features [11]. Thirdly, intact fertility with biologically fathering two children was also noted in our patient who is sufficiently rare for most of LS cases.

Severe form of HCM with early onset of heart failure symptoms and possible sudden death in early infancy is the usual fate with Q510E mutation. So, all patients with the LEOPARD syndrome should undergo periodic cardiac assessment with echocardiography and electrocardiographic examination because the heart conduction impairment tends to occur gradually but progressively. Of note, three previous cases reported by Digilio and Takahashi et al. showed rapidly progressive severe biventricular obstructive hypertrophic cardiomyopathy and structural abnormalities of the mitral valve that caused severe symptoms in very early period of life [8,9]. But our patient uniquely differed on cardiac presentations and had been doing well except for occasional exertional fatigue possibly because of

nonobstructive variety of HCM with asymmetric septal hypertrophy, normal pulmonary and other valves. Although pulmonary stenosis (PS) is a part of the acronym but recently HCM is being observed more frequently in LEOPARD syndrome [7,8]. To compare and contrast the clinical features and phenotypical expressions of present case with that of other LEOPARD syndromes described in the literature, a summary table has been added (Table 1). It is evident from this comparison that with the same genetic mutation, HCM was found in all but pulmonary stenosis was seen in only one case. Similarly, there was variation in the presence of sensorineural deafness. It is logical to speculate that mutation involving a developmental gene like PTPN11 that affects different nuclear signaling pathways is likely to have varying phenotypic expressions.

LS belong to the neuro-cardio-facio-cutaneous syndromes (NCFCs) family. The most prevalent disorders of this group are Noonan syndrome and Neurofibromatosis-1 (NF1), while LS is a rarer condition. NCFCs display significant genetic and phenotypic heterogeneity with common clinical features such as psycho-motor delay, facial dysmorphism and cardiac, cutaneous and skeletal abnormalities. Although genetic causes of NCFCs are heterogeneous, the molecular mechanisms involved alter the RAS/MAPK signaling pathway [12]. RAS is a human oncogene implicated in different cellular functions and its transducing signal, involving different MAP kinases, is critical for cell proliferation and survival. Thus its disruption may result in uncontrolled cell growth and cancer. In contrast, germ-line mutations, which result in a less dysfunctional gene product, underlie the development of NCFCs. So the variations in clinical manifestations encountered in a few recent cases including ours can be hypothesized well with the nature of the gene and its affected protein products. We believe that germ line mutation of a developmental gene can have this kind of pleiotropy and further functional analysis can reveal the actual underlying mechanisms.

Regarding genital abnormality, cryptorchidism is common (seen in ~50% cases) in LEOPARD syndrome [3], as was also evident in our patient but nothing is mentioned about its presence or absence in three other cases that we have considered for comparison. Another interesting finding in our case was his intact fertility fathering two children revealed from paternity testing. Further, parents and siblings of the proband were found to be phenotypically normal and negative for the mutation indicating that the present case is not of familial origin rather sporadic which is relatively rare for LS [8].

Until recently only 200 cases of LS have been described in the literature and to date this is the first clinical report on LEOPARD syndrome with some unique presentations from this locality. We believe that the characteristics including variation in phenotypic presentations noted in the present case will add up on the existing information of this

**Table 1:** Comparison of phenotypic characteristics of case in presentation with recently described cases of LEOPARD syndrome

Clinical features	Present case	Digilio et al. (2002)	Digilio et al. (2002)	Takahashi et al. (2005)
		No. of case 1	No. of case 2	No. of case 1
Sex	Male	Female	Male	Male
Age at presentation	36 yrs	24 months	27 months	14 months
Facial anomalies	+	+	+	+
Hypertelorism	+	+	-	+
Palpebral ptosis	-	+	+	-
Dysmorphic ears	-	+	+	+
Hypertrophic cardiomyopathy	+	+	+	+
Mitral valve anomaly	-	+	-	+
Pulmonary stenosis	-	-	+	-
Thorax anomalies	+	+	-	-
Deafness	-	-	-	+
Skin anomalies	+	+	+	-
Café-au-lait spots	+	+	+	-
Lentigenes	+	+	-	-
Delayed milestones	-	+	+	+
Hypotonia	-	+	+	+
Cryptorchidism	+			

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rare genetic disease and encourage biological and clinical scientists to explore more about its genotype-phenotype correlations.

### Conflict of interest

The authors declare no conflict of interest.

### Consent statement

Oral informed consent was obtained from the patient for publication of this case report and accompanying images

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