Reviewer's report

Title: MAPK activation in mature cataract associated with Noonan syndrome

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Reviewer: Alexsandra C Malaquias

Reviewer's report:

This paper described one patient with Noonan syndrome caused by PTPN11 mutation and association with mature cataract that required surgery. The results could be important in the clinical management of patients with this syndrome.

Major compulsory revisions:

1- The relevant literature is not described fairly adequately:

The authors should explain that mutations in PTPN11, KRAS, NRAS, SOS1, RAF1, BRAF, SHOC2, MEK1, and CBL genes were identified in NS or closely related conditions, comprising Noonan syndrome with multiple lentigines (NS/ML, also termed LEOPARD syndrome), Noonan-like syndrome (NLS) with loose anagen hair (NS/LAH) and the recently documented “CBL mutation associated” syndrome. Noonan-like syndromes comprising Costello syndrome, cardiofaciocutaneous syndrome, neurofibromatosis type 1, and Legius syndrome are disorders clinically related to NS and also harbor mutations in HRAS, KRAS, NF1, BRAF, SPRED1, MEK1, and MEK2 genes. Because of the similar molecular mechanisms disturbing the RAS/MAPK signaling pathway and clinical overlap, NS and these NLS are now grouped as Ras-MAPK syndrome or Ras-opathies.

2- What is the mechanism of onset of cataract? What is the link with Ras-MAPK pathway? This information should be given in the manuscript.

3- The methods are not described with enough detail:

What mutation the patient is affected by? This could be important for others patients with the same mutation.

Minor essential revisions:

1- Case report was confusing! The information about the patient should be in chronological order. Physical exam with relevant characteristic for Noonan syndrome should be emphasized. Final height is missing. Did the patient receive treatment with growth hormone?

Discretionary Revisions:

1- I suggest that nothing should be said about Turner syndrome and similar phenotype - this is a confounding point.

2- I suggest that van der Burgt score must be used for the diagnosis of Noonan
syndrome.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests