Reviewer's report

Title: Diagnosis of Noonan syndrome and related disorders using Target Next Generation Sequencing.

Version: Date: 25 November 2013

Reviewer: tawfeg ben-omran

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This is an interesting manuscript reporting the use of Target Next Generation Sequencing (NGS) in diagnosis of Noonan syndrome and related disorders in a group of 80 patients. Using NGS technology, the authors were able to determine 38 causative mutations in 6 of 11 RAS-pathway genes in 37 patients; however, the remaining 43 patients enrolled in this study were negative for the investigated RAS genes. The manuscript is well written and the method is robust and very well suited to search for pathogenic mutations in such genetically heterogeneous disorders with overlapping, non-specific features that make targeting a specific gene difficult or sometimes impossible. Nonetheless, I believe that the use of this approach should be coupled with more careful clinical evaluation clinical and more strict inclusion criteria. I do not have any major concern about the manuscript.

Comment 1: Minor comments
Under Discussion:
Page 10: (paragraph 3 line 8) the authors stated that "In one patient (case no.16) we identified two unpublished mutations affecting two consecutive of PTPN11 aminoacids, D395Y and Y396H. Both mutations were inherited from an affected father. Variability of clinical expression in this family was quite obvious, since only the son manifested NS facial anomalies and developmental delay while the father had congenital total alopecia." This part deserves more elaboration and discussion.