## Factsheet MAP2K1

<table>
<thead>
<tr>
<th>Centogene ID</th>
<th>161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene(s) name (OMIM, HGNC):</td>
<td>MAP2K1</td>
</tr>
<tr>
<td>Gene OMIM:</td>
<td>176872</td>
</tr>
<tr>
<td>Disease name</td>
<td>Noonan syndrome</td>
</tr>
<tr>
<td>Disease OMIM:</td>
<td>115150</td>
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<tr>
<td>Gene location:</td>
<td>15q22.31</td>
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</tbody>
</table>

### 1. Disease synonyms
Cardio-facio-cutaneous syndrome; CFCS; MAP2K1-related Noonan Syndrome

### 2. Material

<table>
<thead>
<tr>
<th>minimum DNA (µg)</th>
<th>minimum EDTA blood (ml)</th>
<th>minimum filtercards (pcs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
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</table>

### 3. Turnaround time

<table>
<thead>
<tr>
<th>single exon testing (working days)</th>
<th>full gene sequencing (working days)</th>
<th>with del/dupl analysis (working days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>25</td>
<td>45</td>
</tr>
</tbody>
</table>

### 4. Inheritance pattern
Autosomal dominant

### 5. Clinical features
Germline mutations in the MAP2K1 gene have been reported to be associated with two distinct syndromes: Noonan syndrome and cardiofaciocutaneous (CFC) syndrome. These syndromes share a common pattern of congenital anomalies, including typical heart defects, overlapping craniofacial dysmorphisms, short stature, and a variable degree of intellectual disabilities.
Noonan syndrome (NS) is an autosomal dominant syndrome characterized by short stature, congenital heart defect, and developmental delays of variable degrees. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, ocular abnormalities, and deafness. Characteristic facies include hypertelorism (74%), downward sloping palpebral apertures (38%), epicanthal folds (39%), ptosis (48%), and low-set posteriorly rotated ears. Early feeding difficulties such as difficulty sucking or gastrointestinal dysfunction, are also common. Although birth length is usually normal, final adult height approaches the lower limit of normal. Up to one-third of affected individuals have mild intellectual disabilities. Congenital heart disease occurs in 50%-80% of individuals with NS. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of the individuals. Hypertrophic cardiomyopathy is found in 20%-30% of individuals, and may be congenital or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. NS is clinically diagnosed. Affected individuals have normal chromosome studies. Molecular genetic testing identifies mutations in PTPN11 in more than half of affected individuals, KRAS in fewer than 5% of those affected, SOS1 in approximately 13%, and RAF1 in 3%-17%. Mutations in the MAP2K1 (15q21) gene have been reported in less than 1% of all cases. Many affected individuals have de novo mutations; however, an affected parent is recognized in 30%-75% of families. When the parents are clinically unaffected, the risk to siblings appears to be low (<1%).

Cardiofaciocutaneous (CFC) syndrome is characterized by features in three primary systems: cardiac, craniofacial, and ectodermal; however, other systems may be involved as well. Cardiac abnormalities can include pulmonic stenosis and other valve dysplasias, septal defects, hypertrophic cardiomyopathy, and rhythm disturbances. Individuals with CFC syndrome have a distinctive craniofacial appearance. Ectodermal features include skin findings, such as xerosis, hyperkeratosis, ichthyosis, keratosis pilaris, ulerythema oophorogenes, eczema, pigmented moles, palmoplantar hyperkeratosis; hair findings such as sparse, curly, fine or thick, woolly, or brittle hair, and possible absent eyelashes and eyebrows; and finger or toenails may be dystrophic or display rapid growth. Cognitive delay (ranging from mild to severe) is seen in all affected individuals. Neoplasias have been reported in some individuals with CFC. There are four genes known to be associated with CFC. Mutations in the BRAF gene account for ~75% of cases, those in MAP2K1 and MAP2K2 account for ~25% of cases, and those in KRAS accounts for <2% of cases. CFC syndrome is inherited in an autosomal dominant manner; however, most cases of CFC syndrome arise de novo. Please note this is for the MAP2K1 gene only. For patients with suspected MAP2K1-related disorders, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

6. Differential diagnosis

Turner syndrome, found only in females, is differentiated from Noonan syndrome (NS) by demonstration of a sex chromosome abnormality on cytogenetic studies in individuals with Turner syndrome. The phenotype of Turner syndrome is actually quite different than that of NS, when one considers face, heart, development, and kidneys. In Turner syndrome, renal anomalies are more common, developmental delay is found much less frequently, and left-sided heart defects are the rule.

Watson syndrome is characterized by short stature, pulmonary valve stenosis, variable intellectual development, and skin pigment changes and it also overlaps with neurofibromatosis type 1, however it has a different genetic background.
Costello syndrome shares features with both NS and CFC, and it can be differentially diagnosed only using molecular testing for the PTPN11 and HRAS proto-oncogene.

Noonan-like syndrome with loose anagen hair is caused by mutations in the SHOC2 gene. Neurofibromatosis type 1 (NF1) shares some features with NS, including short stature, learning difficulties, and café au lait patches, but it has a specific molecular background and additional characteristic clinical features.

7. Diagnostic strategy
For all affected individuals who fully meet the clinical criteria, we offer the following diagnostic strategy:

**Step 1:** Sequence analysis/mutation scanning of entire coding and flanking intronic regions of the gene

**Step 2:** If no mutation is identified, deletion/duplication analysis may be considered, using MLPA method (MLPA Holland) and/or qPCR

**Step 3:** If a mutation is identified, further genetic mutation identification is provided using sequencing of the specific mutation carrying exon.

8. Referral reasons
The following individuals are candidates for this particular gene testing:

- Individuals with a family history of disease and presentation of the most common symptoms
- Individuals without a positive family history, but with symptoms resembling this disease
- Individuals with a negative but suspected family history, in order to perform proper genetic counseling (prenatal analyses are recommended in families with affected individuals).

9. Test utility
Sequencing, deletion/duplication testing of this gene and related genes should be performed in all individuals suspected for this particular phenotype. In parallel, other genes reported to be related with this clinical phenotype should also be analyzed for the presence of mutations, due to the overlap in many clinical features caused by those particular genes.

Confirmation of a clinical diagnosis through genetic testing can allow for genetic counseling and may direct medical management.

Genetic counseling can provide a patient and/or family with the natural history of the condition, identify at-risk family members, provide reproductive risks as well as preconception/prenatal options and allow for appropriate referral for patient support and/or resources.

10. References