

Future prospects for treatment of Noonan syndrome spectrum disorders

Dr Emma MM Burkitt Wright

Consultant Clinical Geneticist

Manchester Centre for Genomic Medicine



Manchester University
NHS Foundation Trust

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A diagnosis of Noonan syndrome

- Can be a big deal!
 - Some people can have severe manifestations, particularly heart or lymphatic, or if their pattern is more towards CFC end of the spectrum
 - Complications may occur, most often in early life
 - Getting any diagnosis can be a significant time
 - Implications for the future?
 - A good explanation for differences someone already has?
- But may not be associated with any problems

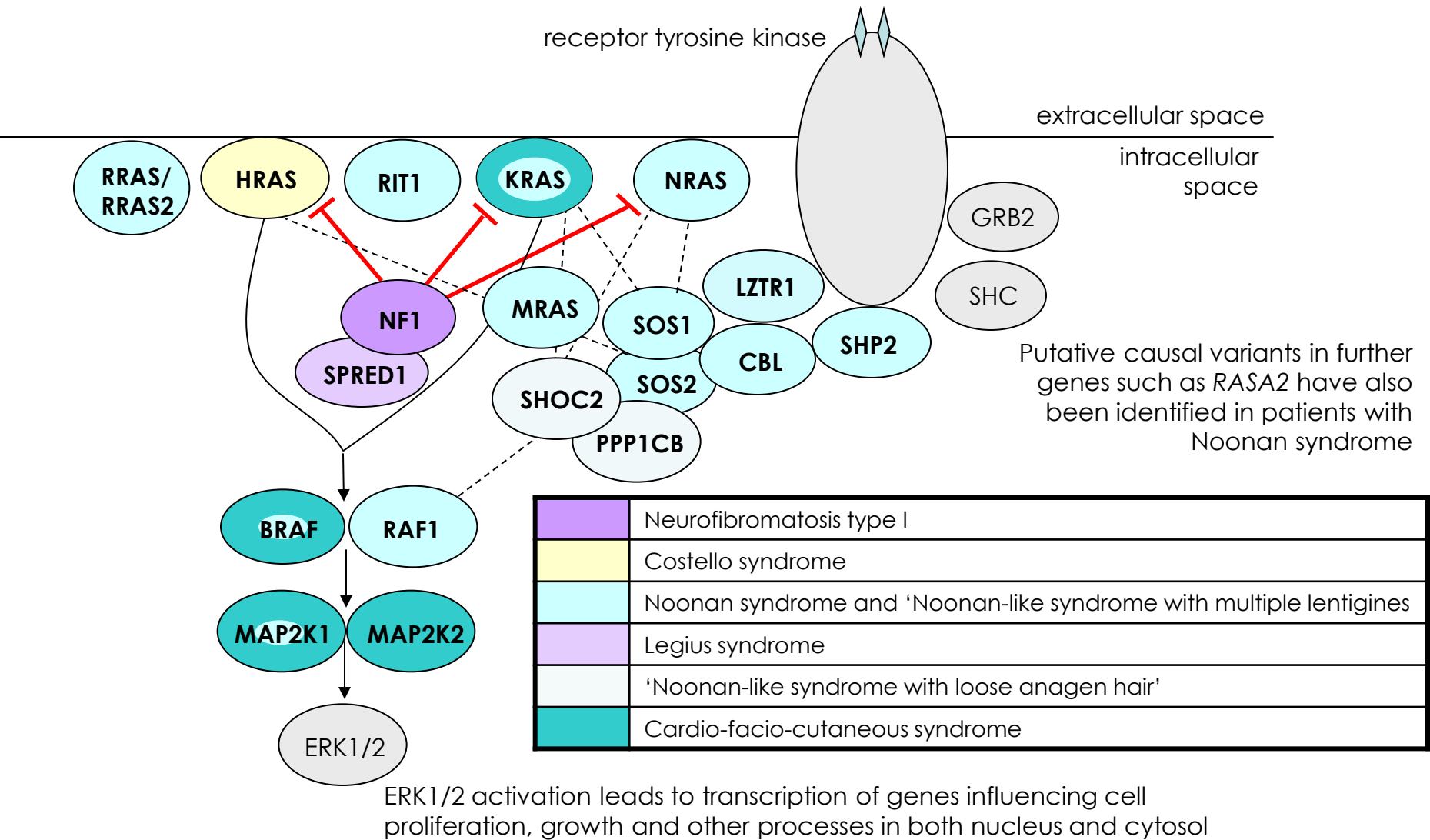
Knowledge is power:

- Alertness for complications
 - Knowing that many are rare
- Appropriate health advice
 - Extra checks, or can be released from extra investigations
- An explanation for differences
- A key to unlock resources and support
 - Targeted treatments?

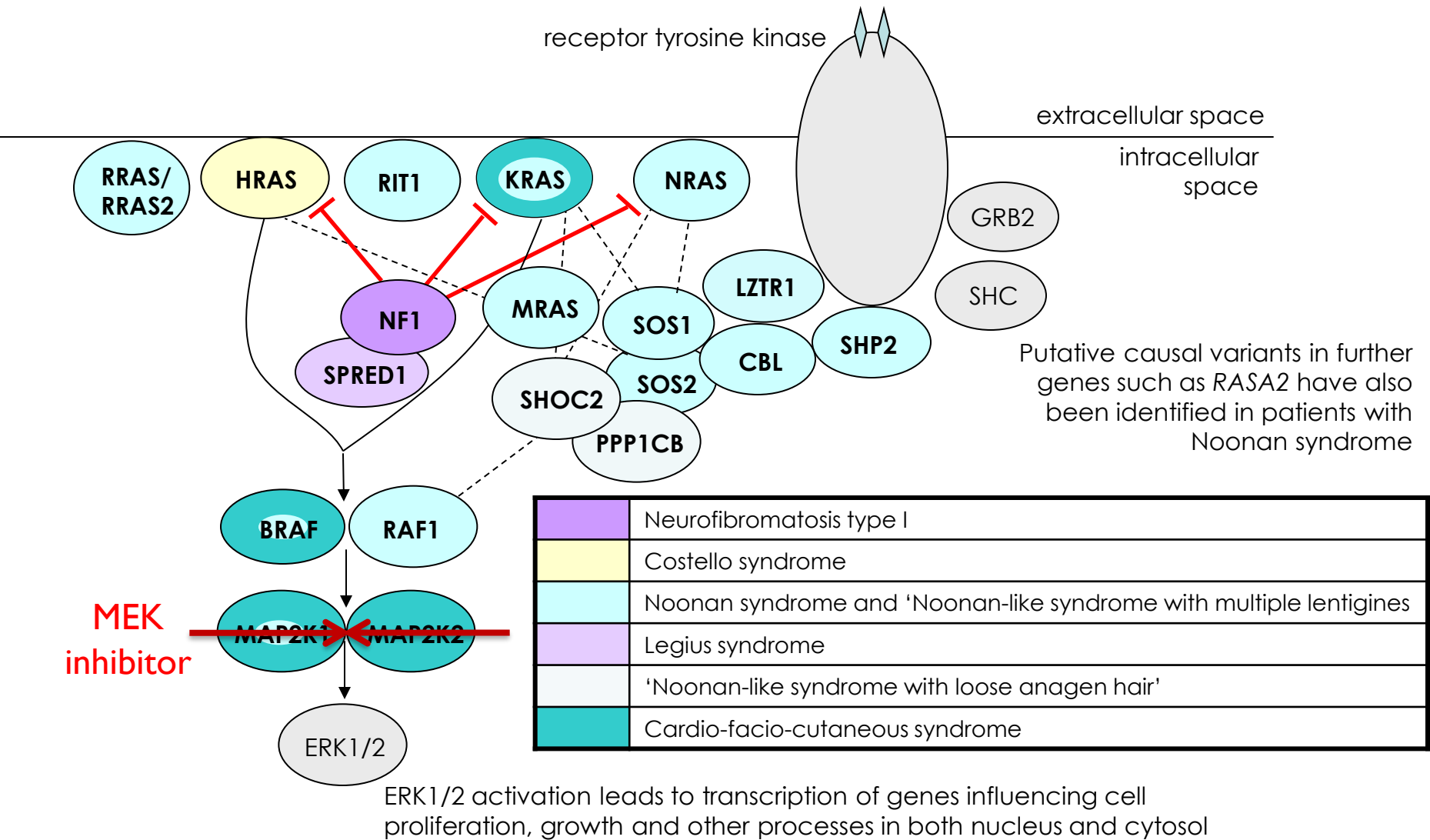
Knowledge is power:

- For many people, especially once grown up, neurobehavioural features are their biggest daily effect from Noonan syndrome
 - Advocacy: getting appropriate support
 - Possibility of contact with other people with NS

Germline disorders of the Ras-MAPK pathway



Germline disorders of the Ras-MAPK pathway



Medical complications

- Cardiovascular issues
 - Congenital heart disease
 - **Hypertrophic cardiomyopathy**
 - **lymphoedema**
- Feeding and other GI issues
- Neurological differences
 - **Epilepsy?**

Noonan syndrome: 1 in 2000 people?

- Short stature
- Pulmonary stenosis and other CHD; HCM
- Feeding problems
- Curly hair, ptosis, blue irides, posteriorly rotated ears
- Undescended testes
- Mild LD, autistic spectrum disorder etc
- Lymphatic problems
- Bone marrow problems - JMML
- Bleeding/bruising



Noonan syndrome: genotype-phenotype correlations

PTPN11

- 50% of people with Noonan syndrome
- ‘Noonan syndrome with multiple lentigines’ (specific changes in *PTPN11*)

SOS1

- Short stature and learning differences less common than in *PTPN11*- associated NS
- Skin and hair features prominent
- More commonly inherited

Noonan syndrome: genotype-phenotype correlations

RIT1

- Often normal height and learning; 10% of total
- High rate of HCM
- Lymphatic anomalies

RAF1

- HCM, arrhythmias...

SOS2

- Lymphatic anomalies, nerve enlargement (rare)

Knowledge is power:

- If we know the exact gene change responsible for a person's presentation
 - Diagnosis is confirmed
 - May give information about chances of complications
 - Particularly important in early life
 - In future, might help us know if particular treatments may be effective

Summary

- For many people with NS, no specific management will be needed
- For many people with NS-related differences, management will be as for these occurring in the general population
 - Two-way knowledge exchange!
- Specific Noonan syndrome spectrum related complications may benefit from targeted treatment such as MEK inhibitors

**Noonan Syndrome Association, Costellokids,
Costello Syndrome Family Network, CFC International...**

Colleagues in MCGM

NSS consensus management guidance collaborators:

Sarah Wilson, Bronwyn Kerr, Ian Legg,
Martin Zenker, Marco Tartaglia, Alain Verloes,
Bruce Gelb and so many others...

