

## Noonan Syndrome

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## History

- The condition is named after Dr Jacqueline Noonan an American cardiologist who only retired in 2007.
- She noticed that many of the children with a certain unusual heart defect, pulmonary valvular stenosis, often looked similar to one another.
- They were short, sometimes had a webbed neck, widely spaced eyes and low set ears.
- Both boys and girls were affected.
- Even though these characteristics were sometimes seen running in families, the chromosome test was always normal

Albrect  
'Among  
those  
left'

## How common

- Approximately 1 in 1,000 to 1 in 2,500 children worldwide are born with Noonan Syndrome or one of the related conditions.
- It is one of the most common genetic conditions associated with congenital heart disease.
- The range and severity of features can vary greatly and many cases are missed
- Therefore, the syndrome is not always identified at an early age.

## 12 year old girl

- From the original publication
- By Dr Noonan

## Making the diagnosis

- Despite identification of four causative genes when first publications came out (more now), the diagnosis of Noonan syndrome is still a clinical one.
- That means that it is made when the physician considers that the child has enough of the characteristic features to warrant the label Noonan syndrome (or one of its variants)
- DNA testing now confirms most cases

## The “look” that makes the diagnosis

## The genes

- We can test the patient for mutations in the PTPN11, SOS1, KRAS, SHOC2, RIT1 etc genes
- But if we don't find a mutation, will not exclude the diagnosis as there are more as yet undiscovered genes that cause these conditions.
- Why make the diagnosis?
- it guides additional medical and developmental evaluations
- excludes other explanations for the features
- allows accurate genetic counselling for families
- *More about genes later...*

## Features seen in NS

- Short stature
- Congenital heart defect often PVS
- Broad or webbed neck
- Unusual chest shape - pectus carinatum and or pectus excavatum
- apparently low-set nipples
- developmental delay to a variable degree
- Undescended testes-cryptorchidism (in boys)
- Characteristic facial appearance

## Facial appearance: Infancy

Cute!

Short uptilted nose

If fair complexioned

Sometimes really blue eyes

Set wider apart than normal

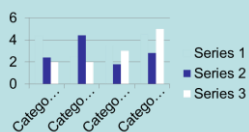
## Face of the toddler

## A bit later

As a baby ...

Same boy aged 11 – curly hair!

School age



Emilia

Chilean  
background  
KRAS mutation  
found

## Heart problems

- Congenital heart disease 50%-80%
- Pulmonary valve stenosis -most common 20%-50%
- Hypertrophic cardiomyopathy 20%-30%
- May be present at birth or infancy/childhood
- Other structural defects:
  - atrial and ventricular septal defects
  - branch pulmonary artery stenosis
  - tetralogy of Fallot
- ECG can be abnormal (even in structurally normal heart) in >87%

## Broad or webbed neck

Low posterior hairline (55%)

Short, broad neck with webbing more obvious in later childhood

## Abnormal Chest shape

- Superior pectus carinatum
- Inferior pectus excavatum
- Apparently low-set and widely spaced nipples

## Behaviour

- Children perform well in normal setting
- No particular syndrome of behavioural disability or psychopathology is observed
- Autistic features not generally seen
- Self-esteem is comparable to age-related peers
- These children are well liked
- Alexithymia sometimes present cant identify emotions in others

SOS 1  
mutation

## Psychomotor development

- Many children with Noonan learn normally!
- IQ mostly in normal range - tends to lower end
- Early development may be delayed
- Mild learning disability seen in up to 1 in 3
- 25% have a more significant learning disability
- But...Only 10-15% special education
- I know 2 with PhDs
- Verbal performance often worse than nonverbal
- Articulation problems common 3/4
- This responds well to speech therapy

## Eye problems

- Squint (strabismus)
- Refractive errors (need glasses)
- Nystagmus (jumpy eyes)
- Many have some ophthalmological problem
- Rarer problems
  - optic nerve hypoplasia
  - Coloboma
- Hearing
  - Deafness rare

## Genitourinary

Undescended testes (cryptorchidism)  
60-80%  
male infertility common

Kidney problems  
– generally mild  
– most commonly some outflow obstruction

Delayed puberty

## Skin

- Skin often abnormal esp in CFC
- esp follicular keratosis
- Dryish lumps on arms / face common
- Hair may be curly, thick, and woolly
- or sparse/ poor growing with easy breakage
- Birthmarks on the skin
- Café-au-lait spots, freckles & moles (naevi) more common

## Curly curly hair!

## Haematology

Many of the children have an increased tendency to bleed

Varied causes

Important to mention if surgery is planned!

Rarely causes serious problems

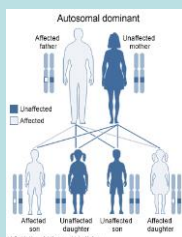
Blood tests can detect

Need to mention if having surgery

## Oncology

- Rare forms of leukaemia are somewhat more common in certain types of NS
- Several reported cases
- Risk still unclear – some mutations more likely
- Worrying but rare!

## How is it inherited?



## The face changes with age

## B & J L

## Facial appearance: adulthood

- **Becomes more triangular**
- **wide at the forehead**
- **tapering to pointed chin**
- **Eyes less prominent**
- **Neck lengthens – can accentuate apparent neck webbing**

## Older adult

- Nasolabial folds are prominent
- skin appears transparent & wrinkled

## Prenatal Noonan

- A number of features may suggest the diagnosis including:
- Increased nuchal test (NT)
- Short long bones
- Pleural effusions (water around the lungs)
- Hydrops/cystic hygroma (seriously swollen fetus)
- Cardiac and renal anomalies

## More on Noonan genes

- Commonest cause of Noonan syndrome (NS1)
- Mapped to 12q24.1 in 2001
- (They knew the gene was in that section of chr 12 but hadn't yet found it)
- Found the gene – called PTPN11 later that year
- Mutations in this gene ~50% NS
- The "Major" Noonan gene

## Other NS genes

- SOS1 gene..... ~ 17%
  - RAF1 gene..... 3%-17%
  - KRAS gene.....very small number
  - Additional genes – some known more to come.
- Mutations in the neurofibromin gene (NF1) in Watson syndrome (neurofibromatosis-Noonan)
- Explains why some people with NF look a little Noonan-like

## PTPN11

- *PTPN11* mutns often with pulmonary stenosis
- Cardiomyopathy less common in *PTPN11*
- Linked to short stature, pectus deformity, easy bruising, characteristic facial appearance and cryptorchidism
- At least one mutation (N308D) more likely to have normal education
- Specific mutations associated with risk for a rare leukaemia

## SOS1 mutations

- 10-20% Noonan syndrome
- Next commonest NS gene
- NS with SOS rather like other Noonan syndrome
- more frequently show skin features
- greater likelihood normal developmt/stature
- Cardiac septal defects may be more frequent than in *PTPN11*
- PS more common in SOS pts
- Often not so short (70% in general NS)
- Don't bleed/no incr risk malignancy Often familial

## SOS-1 Noonan

## RAF1

- Highly correlated with hypertrophic cardiomyopathy
- 95% show this feature
- Prevalence in NS generally 18%
- Cardiomyocyte hypertrophy occurs due to ↑Ras signaling
- Leopard syndrome also due to gain-of-function *RAF1* mutns
- ~ 1/3 without *PTPN11* mutns will have mutn in *RAF1*

## RAS-ERK pathway

## Noonan Syndrome

- Not uncommon at all
- Many are missed
- Very variable in it's effects
- Changes with time
- Most have normal IQ
- Gene testing may help guide management
- Boys may need testosterone therapy

His mother, 2 uncles and grandma

Uncle (above)  
surgery for Chiari  
malformation