Trends in Prenatal Diagnosis of Denovo Mutations over a 10 year Period

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- **Main Goal: Help people bring healthy babies**
- **55 workers**
- **60,000 tests every year**
- **More than 2,000 invasive prenatal diagnosis every year**

How do we achieve our goals?

- **Pre Conception Genetic Screening**
- **Genetic diagnosis in families with affected family members**
- **Follow up and consult to pregnancies with suspected genetic diseases detected by imaging, biochemical testing or other methods**

Pre Conception Genetic Screening

- **Thousands of genetic diseases**
- **A couple of dozens relatively common**
- **Most autosomal recessive**
- **One X-linked (fragile X syndrome)**

Pre Conception Genetic Screening

- **In the last 25 years pre -conception genetic screening programs have been founded**
- **The number of diseases being checked is constantly growing**
- **Currently the field is being revolutionized**

Pre Conception Genetic Screening

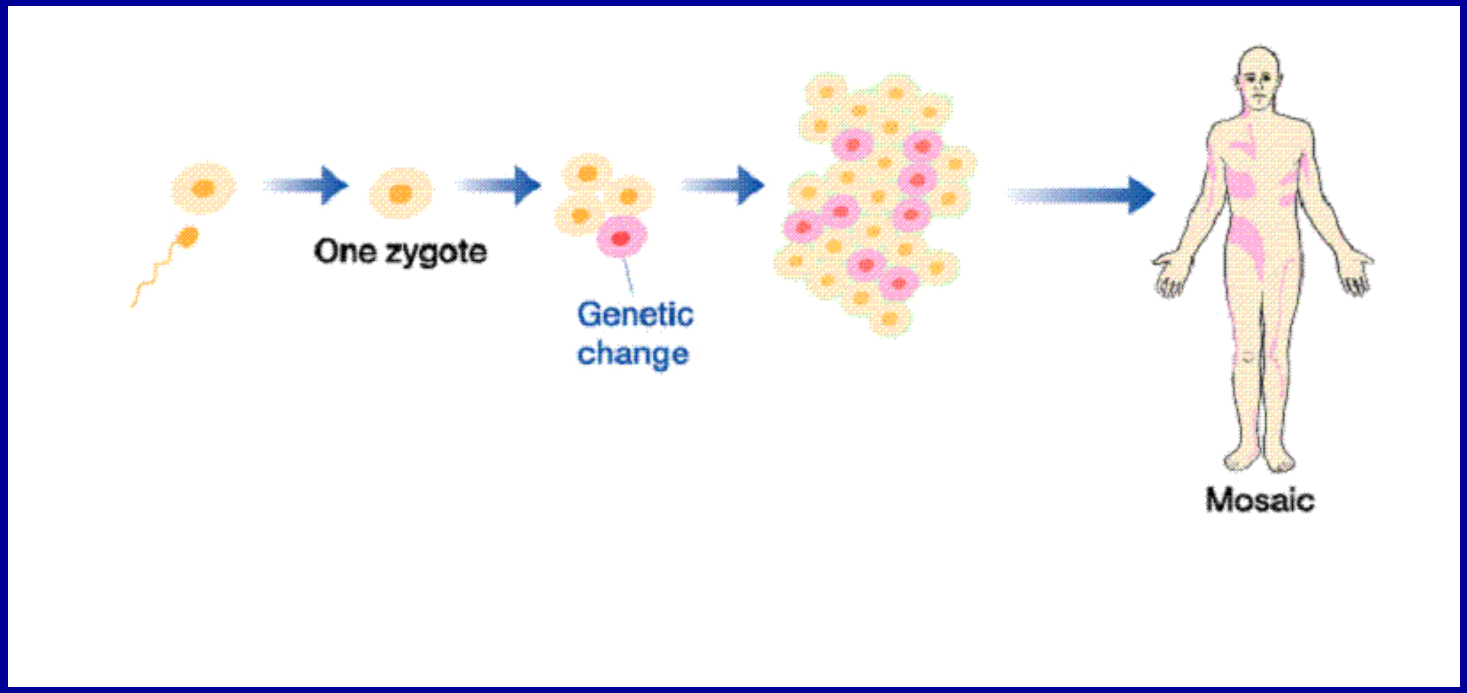
- **Usually the female is first screened**
- **If found a carrier her mate is checked**
- **If both are carriers: PND or PGD**
- **New microarray chips 200-500 diseases**
- **1% are saved from serious problems**

Genetic diagnosis in families with an affected child

- **Clinical assessment and diagnosis**
- **Sequence the suspected disease causing gene**
- **When a number of genes can cause the disease, or when no diagnosis is reached- exome sequencing**

Results of exome sequencing in children with suspected genetic disease

- **Mendelian inheritance (autosomal recessive, autosomal dominant or X-linked**
- **No significant finding**
- **Denovo mutations**


One zygote
Genetic change
Mosaic

Denovo mutations vs. inherited mutations

- The earlier a Denovo mutation occurs, the more cells will be affected and thus the more severe presentation would be
- Some times denovo mutations are so severe the if they affect all of the cells of a given individual he will not be able to survive
- In certain disorders (which involve immune cells continuous replicating cells) denovo mutations can occur at any age.

Denovo Mutations

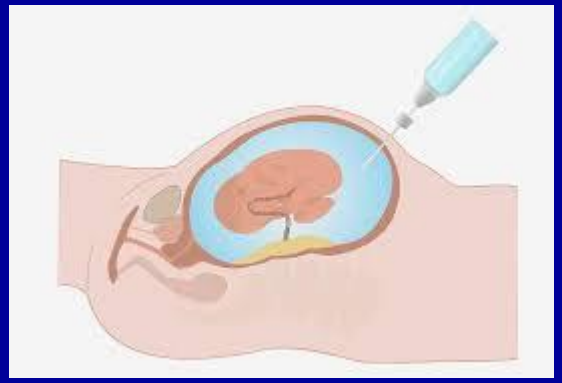
- Rett Syndrome
- Alexanders disease
- Achondroplasia
- Osteogenesis impefecta
- Hemophilia

Recurrence Rate

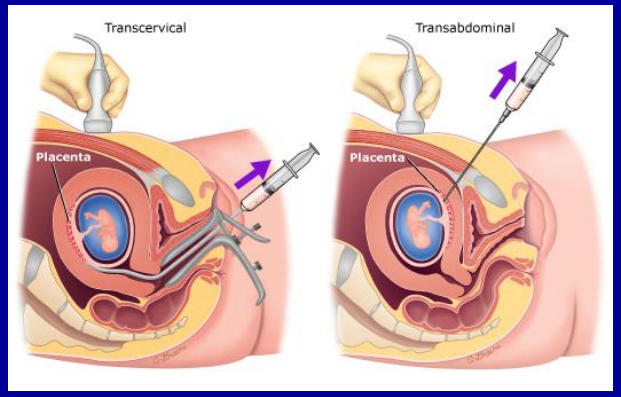
Autosomal dominant	50%
Autosomal recessive	25%
Denovo mutations	1-4%

Prenatal diagnosis

- Amniocynthesis: Week 16-23



- Chorionic villus sampling(CVS): Week 11-12



Prenatal diagnosis for Denovo mutations at the SMC

- In recent years we were under the impression that there is an increase in the frequency of prenatal diagnosis for Denovo mutations

Aim

Check trends in prenatal diagnosis at the SMC for Denovo mutations over a 10 year period:

- Is there a relative or absolute increase in prenatal diagnosis for denovo mutations over a 10 year period.
- Type of diseases being diagnosed.
- Recurrence rate in following pregnancies.
- Age of the father.

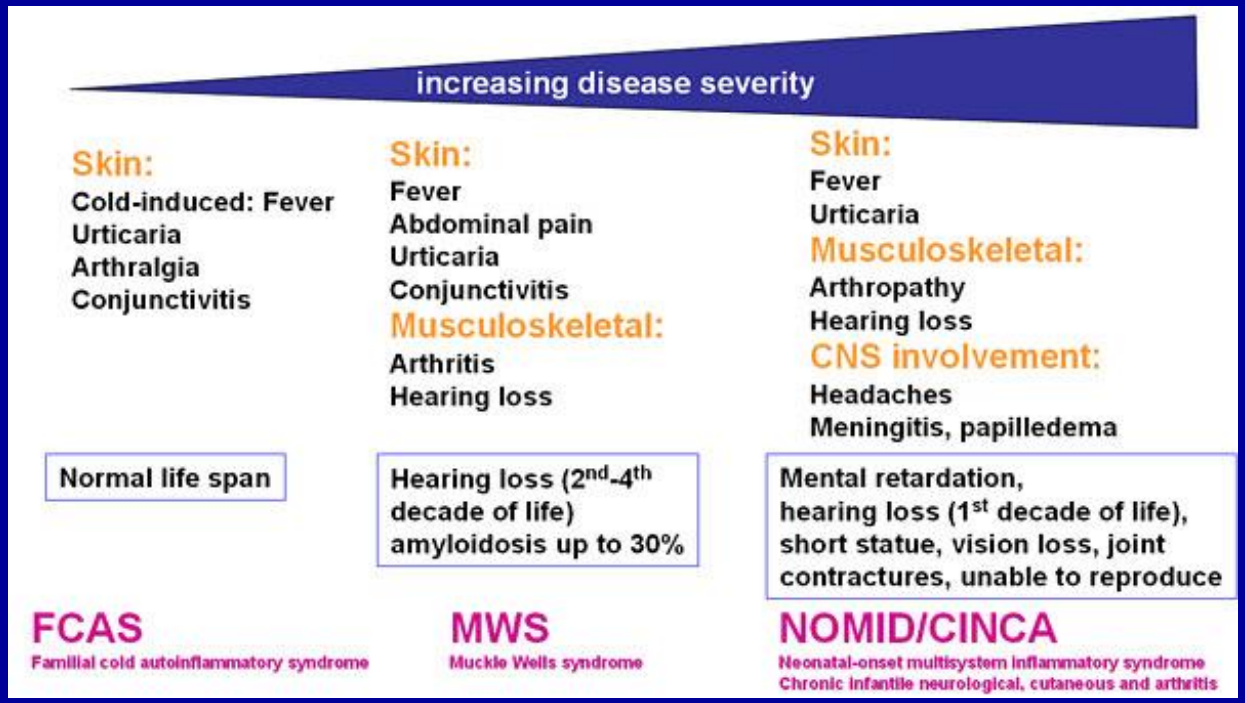
Preliminary Results

- **Over a 10 year period we have performed 100 Prenatal diagnosis for denovo mutations.**

- **10 fold increase over the years**


Thank You

CAPS


increasing disease severity
Skin:
Cold-induced: Fever
Urticaria
Arthralgia
Conjunctivitis
Skin:
Fever
Abdominal pain
Urticaria
Conjunctivitis
Musculoskeletal:
Arthritis
Hearing loss
Skin:
Fever
Urticaria
Musculoskeletal:
Arthropathy
Hearing loss
CNS involvement:
Headaches
Meningitis, papilledema
Normal life span
Hearing loss (2nd-4th decade of life) amyloidosis up to 30%
Mental retardation, hearing loss (1st decade of life), short statue, vision loss, joint contractures, unable to reproduce
FCAS
Familial cold autoinflammatory syndrome
MWS
Muckle Wells syndrome
NOMID/CINCA
Neonatal-onset multisystem inflammatory syndrome
Chronic infantile neurological, cutaneous and arthritis

Brief Report: Late-Onset Cryopyrin-Associated Periodic Syndrome Due to Myeloid-Restricted Somatic NLRP3 Mosaicism.

Mensa-Vilaro A et al,

OBJECTIVE:

Gain-of-function NLRP3 mutations cause cryopyrin-associated periodic syndrome (CAPS), with gene mosaicism playing a relevant role in the pathogenesis. This study was undertaken to characterize the genetic cause underlying late-onset but otherwise typical CAPS.

METHODS:

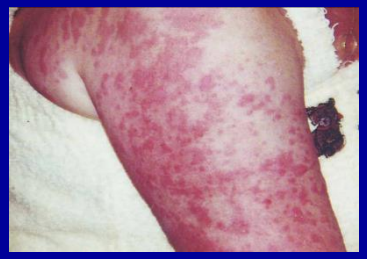
We studied a 64-year-old patient who presented with recurrent episodes of urticaria-like rash, fever, conjunctivitis, and oligoarthritis at age 56 years. DNA was extracted from both unfractionated blood and isolated leukocyte and CD34+ subpopulations. Genetic studies were performed using both the Sanger method of DNA sequencing and next-generation sequencing (NGS) methods. In vitro and ex vivo analyses were performed to determine the consequences that the presence of the variant have in the normal structure or function of the protein of the detected variant.

RESULTS:

NGS analyses revealed the novel p.Gln636Glu NLRP3 variant in unfractionated blood, with an allele frequency (18.4%) compatible with gene mosaicism. Sanger sequence chromatograms revealed a small peak corresponding to the variant allele. Amplicon-based deep sequencing revealed somatic NLRP3 mosaicism restricted to myeloid cells (31.8% in monocytes, 24.6% in neutrophils, and 11.2% in circulating CD34+ common myeloid progenitor cells) and its complete absence in lymphoid cells. Functional analyses confirmed the gain-of-function behavior of the gene variant and hyperactivity of the NLRP3 inflammasome in the patient. Treatment with anakinra resulted in good control of the disease.

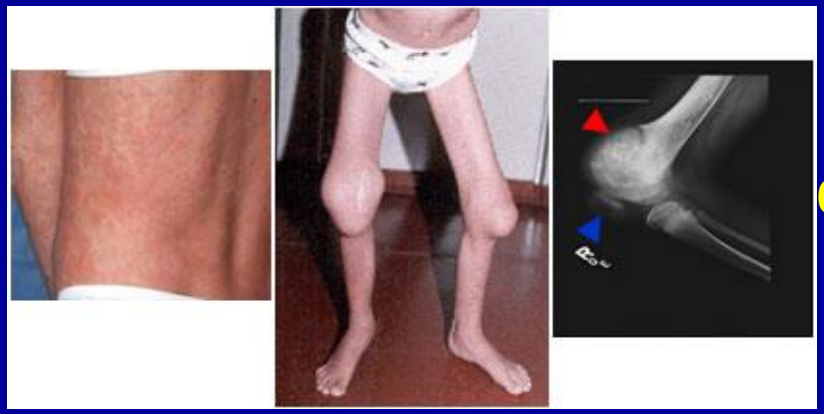
CONCLUSION:

We identified the novel gain-of-function p.Gln636Glu NLRP3 mutation, which was detected as a somatic mutation restricted to myeloid cells, as the cause of late-onset but otherwise typical CAPS. Our results expand the diversity of CAPS toward milder phenotypes than previously reported, including those starting during adulthood.



High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study.

Tanaka N, Izawa K, Saito MK, Sakuma M, Oshima K, Ohara O, Nishikomori R, Morimoto T, Kambe N, Goldbach-Mansky R, Aksentijevich I, de Saint Basile G, Neven B, van Gijn M, Frenkel J, Aróstegui JI, Yagüe J, Merino R, Ibañez M, Pontillo A, Takada H, Imagawa T, Kawai T, Ya a T, Heike T.



625-32. doi: 10.100