TRENDS IN PRENATAL DIAGNOSIS OF DE NOVO MUTATIONS OVER A 10 YEAR PERIOD

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Introduction

- Prenatal diagnoses to identify carriers for autosomal dominant, recessive and x-linked diseases, in order to prevent recurrence.
- A forth and much less common is de novo mutations.
- De novo mutations within the embryo itself or in its parents gametes. Recurrence in a case of de novo mutation is 1-4%, this is due to the risk of one of the parents having a germline mutation.
- Advanced paternal age at the time of conception is the single and most important risk factor contributing for de novo mutations.
- In order to prevent recurrence in such families we offer prenatal diagnosis by amniocentesis between 17-22 weeks of the pregnancy.

Prenatal diagnoses for de novo mutation at SMC

- We summarized the results of 91 prenatal diagnoses performed for de novo mutations over a 10 year period.

Aim

- Check for trends in prenatal diagnosis over a 10 year period.
  - Is there a relative or absolute increase in prenatal diagnosis for de novo mutations over a 10 year period?
  - Type of diseases being diagnosed.
  - Recurrence rate in following pregnancies.
  - Does advanced paternal age play a role in our cohort?

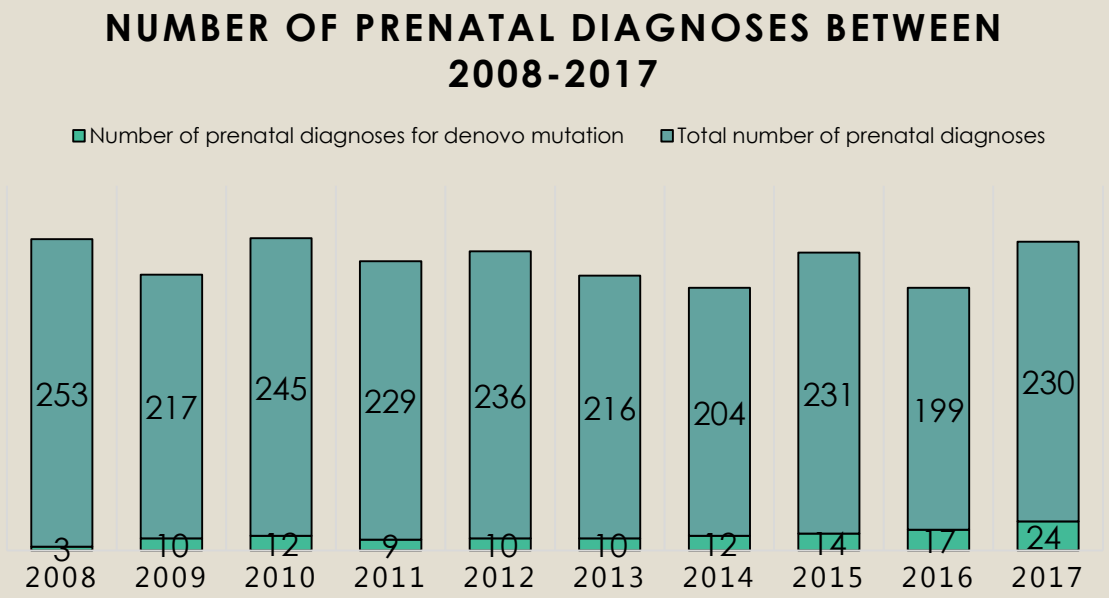
Methods

- Each year we perform about 230 prenatal diagnoses for mendelian disorders (x-linked, dominant and recessive).
- 122 diagnoses were for de novo mutations.
- Total of 91 different families.

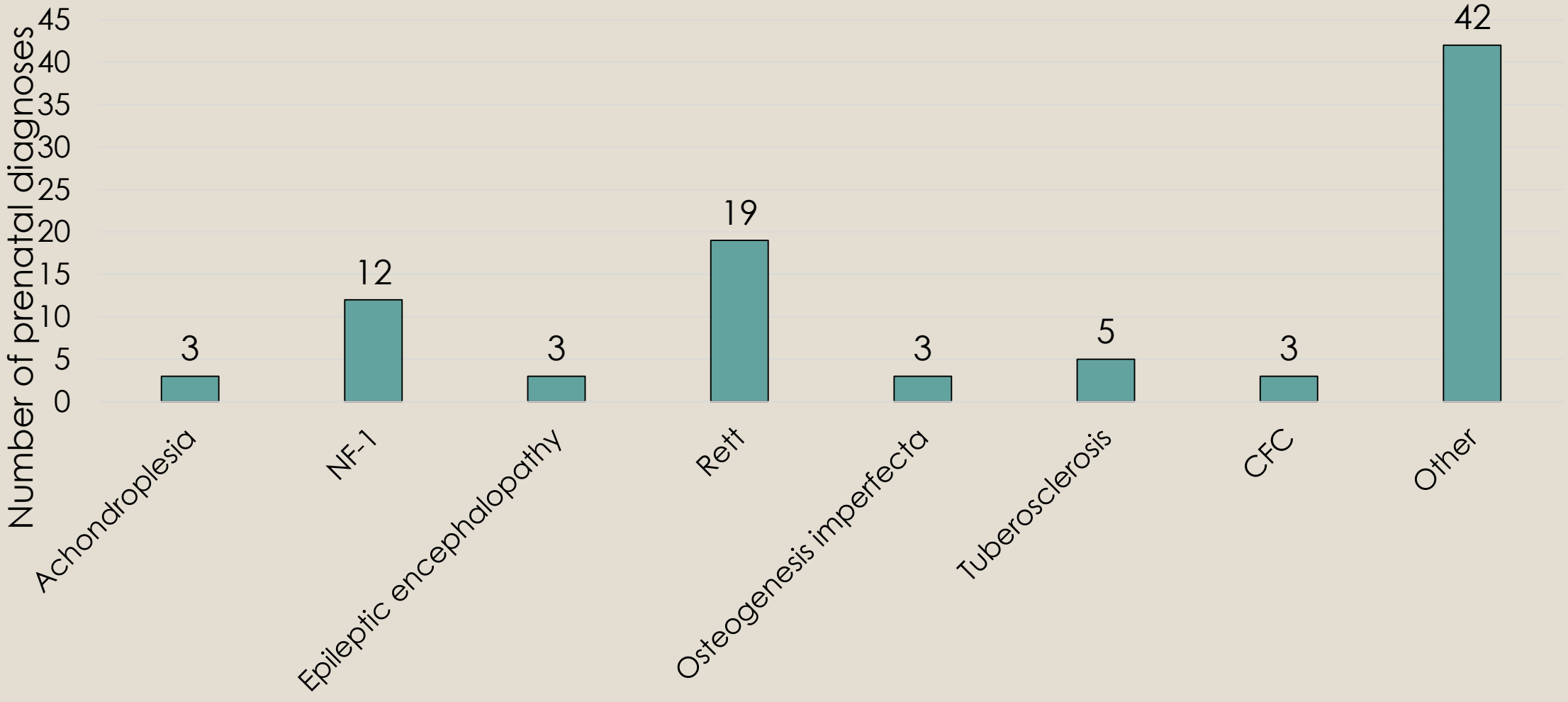
- Control group (to compare paternal age)- Records from the Israeli ministry of health between the years 2008-2015. Total of 1,248,955 live births.

Is there a relative or absolute increase in prenatal diagnoses for de novo mutations over a 10 year period?

- In 2008 the total number of prenatal diagnoses for de novo mutations was 3.
- In 2017 the total number of prenatal diagnoses for de novo mutations was 24.
- Average number of diagnoses per year remained about the same- approx. 230 per year.
- Overall, an 8-fold increase.



Common syndromes



Hotspot mutations

- Mutational hotspots are the probable explanation of the recurrence of the same mutations in a number of genes in different families in our cohort.

syndrome	Most common mutation (number)
Achondroplesia	G380R (3)
Rett	R168X (6)
Rett	R180X (2)

Recurrence rate

- According to the literature there is a 1-4% recurrence rate of de novo mutations, therefore prenatal diagnosis are offered to families where a mutation was found.
- Recurrence rate in SMC between 2008-2017 is 3.33%. (3 cases out of 91 families).

Syndrome	Mutation	Recurrence rate
Osteogenesis imperfecta	COL1A2- G994D	2 recurrences
Rett	MECP- R294X	2 recurrences
Tuberous Sclerosis	TSC1- R786X	2 recurrences

Paternal age

- Advanced paternal age poses a risk for developing de novo mutations in gonadal cells.
- Compared to the general population, records from the Israeli ministry of health.
- Data on the general population group was collected for the years 2008-2015 (no data on 2016-2017) and compared to the study group between those years.

Paternal age in the study group and in the general population 2008-2015

- Surprisingly, we did not find an advanced paternal age in our cohort

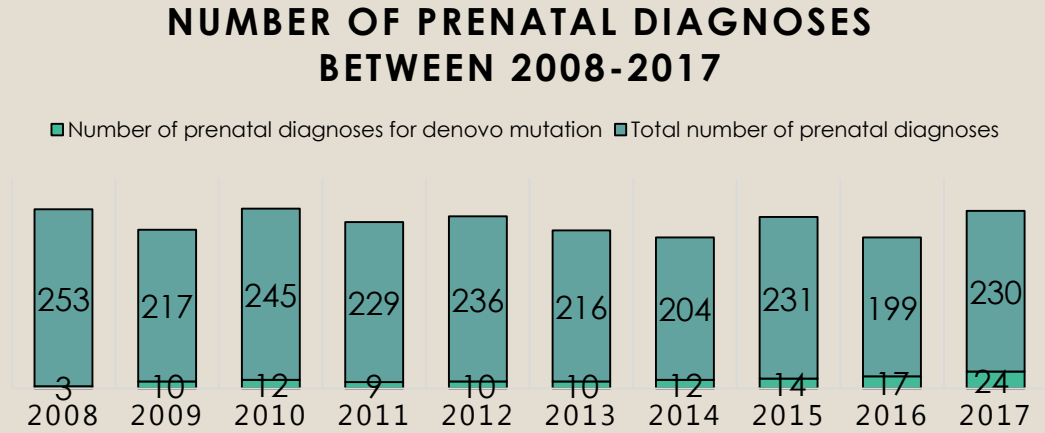
	Average Paternal age	Number of cases	Standard error
Study group	32.37	80	0.3251
General population	32.823	1,248,955	0.0027

Significance- 0.629

Discussion- Why a 8-fold increase in prenatal diagnoses over 10 years?

- **Whole exome sequencing**
  - Technique was introduced about 10 years ago.
  - Most de novo cases in our cohort are diagnosed clinically, without the need of WES

- **Rise in the average parental age**
  - Paternal age plays a role in the creation of de novo mutations according to the literature. However, this is not the case in our study.



Discussion- Why a 8-fold increase in prenatal diagnoses over 10 years?

- **Awareness of the possibility of recurrence among medical staff**
  - Awareness to the possibility of recurrence among couples with a previous pregnancy or child who had a de novo mutation.
  - Along the years more genetic centers were opened making the counseling more available and making medical professionals more knowledgeable on prenatal diagnoses and de novo mutations in general.

- **SMC as a tertiary center**
  - Change in the mix of cases being sent to us as tertiary center
  - More genetic centers

Discussion

- In 3 out of 91 prenatal diagnosis for de novo mutations we detected recurrence of the same de novo mutation, a total of 3.33%. These figures are compatible with previous reports in the medical literature (1-4%).

- The common syndromes seen in our cohort are compatible with the common de novo syndromes according to the literature.

- Mutational hotspots are the probable explanation for the recurrence of the same mutations in a number of genes in different families in our cohort.

Discussion

- We did not find any significant difference in paternal age between our study group and the general population. Two other control groups of CVS and amniocentesis came up with the same result.

RAS-MAPK pathway

- The majority of germline mutations are formed on the paternal allele, due to constant divisions of spermatogonial cells. There is a hypothesis that cells who carry the RAS-MAPK mutation have a growth advantage which leads to their clonal expansion. Paradoxically, despite being detrimental at the organism level, they benefit from a selective advantage in the testis.

- At least 21% of the mutations we found in our cohort are in genes that belong to the RAS-MAPK pathway.

- NF-1 (12)
- CFC (3)
- Achondroplesia (3)
- Tanatophoric Dysplasia (1)

Sub groups of de novo mutations

- De novo mutations can further be divided to include two additional subgroups.
  - Parental mosaicism
  - Postzygotic events in the embryo

- Approx. 4% of seemingly de novo mutations originate from paternal mosaicism detectable in blood samples of one of the parents. Recurrence risk in such cases is higher and has been estimated at above 5%.
- In contrast, about 7% of what may initially appear as de novo mutations arise from postzygotic events in the embryo, thus recurrence risk in those pregnancies is similar to that of the general population.

- Maybe in the future dissecting these two categorize by targeted sequencing in samples from parents and affected offspring may provide a personalized and more accurate estimate of the recurrence risk.

Thanks

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Questions?