PHENOTYPIC AND GENOTYPIC ANALYSIS OF RETT SYNDROME

PhD Thesis

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INTRODUCTION (LITERATURE DATA)

1. Clinical picture

Rett syndrome (RTS, OMIM 312750) is an X-linked neurodevelopmental disorder with an estimated incidence of 1/10000-1/15000. This particular disease seemed to affect only girls got to the centre of interest after the publication of Hagberg's article in 1983. The criteria for the disease determined in 1988 based on international agreement include normal perinatal period, normal head circumference at birth, apparently normal psychomotor development in the first 6 month of age, and afterwards slowing of head growth, loss of hand use, severe speech problem, ataxia, psychomotor delay and stereotypical hand movements.

Although the development seems to be normal in the first months of age (pre-regression), some slight signs can predict the disease such as abnormal muscle tonus, tongue protrusion, abnormal eye and finger movements, hand stereotypes and tremor. The regression starts between 6-18 month of age with loss of speech, ataxic walking, sleeping problems, behavioural changes and autistic signs. Abnormal ventilation pattern and characteristic hand stereotype appear. Other manifestations are epilepsy, joint deformities, scoliosis, osteoporosis and dystrophy (post-regression). During the course of the disease the probability of sudden death is elevated due to the abnormal function of the autonomic nervous system and heart arrhythmias.

Beside the classical phenotype atypical cases are also present such as "forme fruste" or preserved speech variants, and severe forms with early epilepsy.

2. Genetic background

Rett syndrome is inherited X-linked; most of the cases are sporadic but familiar cases are also known. In 1999 mutations in the methyl-CpG-binding protein 2 gene (MECP2) were described in the background of the disease. MECP2 is located on the Xq28 region and encodes a ubiquitous protein (methyl-CpG-binding protein 2: MeCP2). The gene composed of 4 exons has two main functioning domains called methyl CpG binding domain (MBD) and transcriptional repression domain (TRD). The MeCP2 takes part in the building of the histone-deacetylase complex which

represses the transcription of until now unknown genes. Previous studies containing phenotype-genotype correlation analysis conclude that clinical picture of patients with mutation in TRD or nonsense mutation have more severe phenotype than patients with mutation in MBD or missense mutation, however, no strict relationship could be delineated.

Mutation of MECP2 can be found in 50-80% of Rett syndrome patients regarding different studies.

Mutations of MECP2 were rarely demonstrated in boys. More explanations have emerged regarding this issue such as affected boys die in intrauterine or short after birth or the mutations are on the paternal X chromosome which is absent in boys. Plenty of questions emerged about X-linked inheritance that is why all these suggestions are hypotheses.

3. Role of X-inactivation

According to current knowledge X-inactivation may play an important role in the determination of the phenotype of Rett syndrome. According to the Lyon-hypothesis one of the X chromosomes (maternal or paternal) gets inactive in the beginning of embryonic life. Mutation on the active X chromosome can lead to abnormal cell function.

Random X-inactivation means that the maternal and paternal X inactivates in almost equal amount of cells. In the case of non-random (skewed) inactivation the same X inactivates in more than 80% of the cells.

Skewed X inactivation can explain cases of atypical manifestation in spite of disease causing mutation found in MECP2.

In Rett syndrome and other X-linked diseases a higher percentage of skewed X-inactivation was found than in the average population.

4. Function and examination of MeCP2

The basis of therapeutic approaches can only be the proper determination of the effect of the abnormal protein in pathogenesis. MeCP2 attaches to the metilated DNA and plays a key-role in the formation of a “transcription silencing” complex. This complex deacetylates histones and causes condensation of chromatin which in this form is unreachable for transcription factors. MeCP2 has an important role in the early development of the brain. Regarding the function of MeCP2 only few studies exist. It was proved that MeCP2 is expressed in different tissues with different quantity.

OBJECTIVES

1. In our study we analysed the manifestations of Rett syndrome based on detailed clinical approach including anamnesis (questionnaire was constructed), physical examination, skeletal X-ray, orthopaedic, psychological and neurological examination, EEG, and in some cases also cardiologic examination and DEXA. Current work contains the data collected from the questionnaire and physical examination.

2. Mutation analysis of exon 2, 3 and 4 of MECP2 was performed with the aim of the determination of the frequency of mutations in Hungarian Rett syndrome patients.

3. Phenotype-genotype correlation regarding the clinical picture and mutation type was studied.

4. X inactivation in the cases with proved mutation was examined. The frequency of skewed X-inactivation and the possible effect on phenotype was studied.

5. Immune-fluorescent method was used to demonstrate the location of MeCP2 in the cell on fast-proliferating cells (leukaemia cell line), normal human lymphocytes and Rett syndrome patients’ lymphocytes with mutation.

PATIENTS AND METHODS

1. Patients

We started with the prospective clinical and genetic analysis of Hungarian Rett syndrome patients in 2001. At the beginning patients registered in the Hungarian Rett Syndrome Association (22 patients) were involved in the study. After the first results were published patients with the clinical suspicion of Rett syndrome from all districts of Hungary were screened for MECP2 mutations; until now we performed the mutation analysis in 66 girls, in 37 of them we could perform detailed phenotype analysis, as well.

2. Phenotype analysis

Phenotype analysis was performed based on literature data. We summarised the examined clinical signs and the used modified scoring system in Table 1. We examined 22 characteristic feature, based on severity 0-1 or 0-2 point is given; the overall maximal amount can be 39.

Table 1: Phenotype scoring system

Examined parameter	***Point=0***	***Point=1***	***Point=2***
Psychomotor development	normal	normal until 6 month but regression	slow already ≤6 month of age
Start of regression	≥18 month of age	6-18 month of age	≤6 month of age
Head circumference at birth	normal, no slowing of growth	normal but slowing of growth	≤3 centile
Actual head circumference	≥50 centile	25-50 centile	≤3 centile
Body weight	≥10 centile	3-10 centile	≤3 centile
Scoliosis	not exist	exist	operated
Stereotype	never	25-50% of the time	75-95% of the time
Hand use	normal, eats alone	some, eats with help	none
Speech	normal	some syllables	none
Epilepsy	not exist	positive EEG but therapy is not needed	therapy is necessary
Breath	normal	abnormal	not used
Microcirculation	normal	cold hands and feet	not used
Language skill	Some speech	babbles	shouting, no voice
Sleeping problem	not exist	sometimes	pronounced
Motor skill (ability to sit)	≤8 month of age	≥8 month of age	doesn't sit alone
Walking	normal	ataxic	She could never walk or has lost this skill
Start of walking	≤18 month of age	18-30 month of age	≥30 month of age, never
Non-verbal communication	preserved, voluntary	good eye-contact	no eye contact
Muscle tone	normal	slightly abnormal	severely disturbed
Joint contractures	not exist	slight	severe
Mood swing	not exist	exist	not used
Expression and understanding of emotions	not exist	exist	not used

3. Mutation analysis of MECP2 with direct sequencing

Genomic DNA was isolated from blood with a salt-precipitation method (17). The three coding regions of MECP2 were amplified using previously published primer pairs (6). PCR was carried out as following: initial denaturation step (96 ºC, 2 minutes) followed by 35 cycles (96 ºC, 1 min; 55 ºC, 1 min; 72 ºC, 1 min) and a final elongation step (72 ºC, 5 min). PCR products were sequenced bidirectionally By ABI Prism 310 automate sequencer using Big Dye Terminator reagents.

4. X-inactivation studies

We used the androgen-receptor gene test which is based on the polymorphism of CAG trinucleotid repeats in the gene. HpaII is a metilation sensitive enzyme which has cutting position in the androgen-receptor gene. The inactive (metilated) allele remains intact, so only this will be amplified during the PCR process.

Genomic DNA was isolated from blood with a salt-precipitation method. We performed PCR reaction with the patient's undigested and digested (HpaII, MBI FERMENTAS) DNA samples and one of the parent's DNA samples with the following primer pairs:

SBMA-A: TCCAGAATCTGTTCCAGAGCGTGC, and SBMA-B: GCTGTGAAGGTT GCTGTTCCTCAT. PCR was carried out as following: initial denaturation step (95 ºC, 5 minutes) followed by 30 cycles (96 ºC, 1 min; 62 ºC, 1 min; 72 ºC, 1 min) and a final elongation step (72 ºC, 10 min). Detection was performed with 2% agarose gel electrophoresis painted with ethydium-bromide and 8% polyacrilamid gel electrophoresis painted with silver staining method.

The method is not informative if the CAG repeats are similar on both alleles; random inactivation is detected if the pattern of the digested and non-digested DNA samples are the same; non-random (skewed) inactivation is observed if in the digested sample only one of the alleles (the inactive) is present.

5. Immune-fluorescent study

Malignant cells (human pre-B leukaemia), differentiated human leucocytes and proliferating leucocytes were studied.

Malignant cell suspension was centrifuged and washed with PBS. Fixating was performed on room temperature with 1 % formaldehid (10 minutes), then specimen was centrifuged, the supernatant was decanted, and the cells were washed 2 times with PBS and then the specimen was divided into two. To the first we added anti-MeCP2 antibody (Santa Cruz goat antibody, 1:100 dilution, 100 µl), the other was the control. We incubated on 37 ºC for 40 minutes then we washed with PBS. We added to both tube anti-goat FITC-labelled second antibody and incubated on 37 ºC for 40 minutes. We washed with PBS and fixated with 0,1% formaldehid (200 µl). Centrifugation was at all steps with 1200 rpm for 10 minutes.

Differentiated leucocytes were obtained as following: blood in heparin tube was put on Ficoll (1:2) and centrifuged with 3000 rpm for 30 minutes. The mononuclear fraction was washed with 0,9% NaCl and the supernatant was decanted.

Proliferating cells were obtained as following: 5 drop of blood was put on Chromosome medium IA (GIBCO) which is used for routine chromosome analysis. Suspension was incubated on 37 ºC for 72 hours. We centrifuged the tube, decanted the supernatant and added 8 ml 0,05 M KCl to it, and incubated on 37 ºC for 30 minutes, then washed with 0,9% NaCl.

Fixation and the following part of the examination was performed like in the malignant cells with the only difference that for washing we used 0,9% NaCl instead of PBS.

Suspension was dropped on glass-slides, dried and counter-stained with DAPI. Slides were studied with Nikon FXA fluorescent microscope. Flow citometry was done with Partec PAS II type.

RESULTS

1. Clinical examination

According to the classical definition the early psychomotor development is normal but in 25/37 patients' parents told that their child had some symptoms from the following: abnormal posture, tremor, feeding difficulty, failure to thrive, sleepiness, calmness, regardless look or lack of smile.

In more than half of the girls (21/37), motor development was retarded before 6 month. In all cases the head circumference was normal at birth but at the time of examination 28/37 had microcephaly (the head circumference reached the 50th percentile in neither case). Severe dystrophy was observed in 15/37, and small height in 12/37. We found scoliosis in 19/37. The cardinal feature of the disease, stereotypical hand movement was present in all cases but it is not an early sign in most of the cases, it appeared in average at 3 years of age (8 month-6 years). The other classical sign of the disease is the loss of purposeful hand use but in 23/37 of our patients some hand use could be noticed (eat with help, grasp and keep objects for short time). 14/37 of our patients were left handed.

According to our observations speech development follow the characteristic course of normal development and then regression. Most of the girls started to say some words at 1 year of age, then in average at 1,5-2 years of age speech development stopped and regressed, in 32/37 only shouting or babble was maintained. In 18/37 epilepsy appeared, mostly at 4-5 years of age, only in 7 patients started it before 2 years of age. In 5 patients EEG abnormality was observed without manifest seizures. Ventilation problem (e.g. hyperventilation) was presented in 21/37, microcirculation problem in 26/37 and Achilles contracture in 29/37. Muscle tone was abnormal in most of the cases (30/37), truncal hypotonia and hypertonia in extremities was characteristic. Deep tendon reflexes were brisk in some cases but Babinski sign was not present.

We didn't find sleeping problem in 31/37, it can be characteristic in the regression period with behavioural changes.

One of the most typical features is abnormal walking, it is delayed or the child doesn't learn to walk in 22/37; in all patients who could walk ataxia was observed. 12/37 couldn't sit.

A distinctive sign of Rett syndrome is that the children express their feelings and understand the feelings of their surrounding; they express themselves with the help of non-verbal communication like eye contact. However, they don't mimic gestures. Mood instability was observed in 21 cases.

In phenotype analysis the age has an important role because some features like scoliosis or epilepsy appear only in older age and some features like sleeping problems and behavioural changes can be found only in early childhood. We divided our cases into two groups (Table 2); to younger and older than 6 years of age (decimal age was counted). Our youngest patient was 1,7, the oldest was 21,2 years old. The lowest phenotypic score was 11, the highest was 33. Under the year of 6 the average score was slightly lower than in the older patients, 20,4 and 23,2, respectively.

We found no characteristic dysmorphic feature, most of the girls had harmonic face; their look didn't suggest the severe mental retardation which they had. Face asymmetry, small hands and feet and wide first incisors were present in some patients. In most of the patients high-arched palate could be found.

In 11 cases control examination was done 1-3 years after the first one, in most of the cases the status was stagnated, in some girls worsened.

Based on our phenotype analysis it is worth to perform the mutation analysis of MECP2 in every patient with 20 or higher point with this scoring system. If the score is lower but the characteristic stop of speech and ataxic walking is present the diagnosis is also likely. Hand stereotype is not an early sign so lack of it doesn't exclude the disease.

2. Mutation analysis

We performed mutation analysis of MECP2 in 66 cases; in 32 of them (48%) mutation was detected. However, using the phenotype scoring system we could confirm the diagnosis only in 42 patients, 32/42 means then a 78% hit. We found eleven earlier published mutations in 24 patients; we detected novel mutation in eight cases (S134P, T203M, 276insG, 710delG, 1157del32, 1160del7, 1163del35, 1121del191; 1322del9).

In cases where no mutation was detected the role of exon 1 of MECP2 or other genes such as the currently described CDKL5 can come up. Differential diagnostically Angelman syndrome must be mentioned because of the overlapping symptoms. We performed FISH analysis of the critical region of chromosome 15 and uniparental disomy examination in all negative cases but we didn't find any alteration.

3. Phenotype-genotype correlation

In 28/37 patients who were included in detailed phenotype analysis mutation was detected in MECP2 (Table 2). Direct relationship was not found between the mutation type and phenotype but some characteristics could be connected with mutation types (Table 3). Regarding mutation type we divided our patients into four groups (1. nonsense, 2. missense, 3. deletion in exon 4, 4. no mutation). In nonsense mutations we more frequently observed dystrophy, scoliosis and severe microcephaly. In missense mutations short stature was more common. In cases with deletion in exon 4 the movement delay was present at the age of 6 month, most of them couldn't sit at the time of examination, ventilation problem was present in all children, hand use was worse than in other groups, and epilepsy and mood instability was also more frequent. We observed eye problem (e.g. strabismus) only in this group.

We couldn't find mutation in 9 patients but the clinical picture was suggestive for Rett syndrome. In this group the most common sign was the severe delay of movements; they started to walk only at the age of about 5, or most of them never walked. This observation of this phenotype distinction can suggest the possibility that this group of patients compose a new entity.

4. X-inactivation studies

We could perform X-inactivation examination in 23/28 patients with detailed clinical data and mutation in MECP2. In 7 cases the examination was not informative, in 5 patients (~22%) random, and in 11 patients (49%) non-random X-inactivation was found. From the 11 patients with non-random inactivation 10 patients (91%) had skewed inactivation of the paternal X-chromosome. Literature data emphasize that in sporadic cases the mutation is located on the paternal X chromosome. In our patients with deletion in exon 4 random X-inactivation was found.

5. MeCP2 immune-fluorescent studies

We found higher signal intensity in malignant cells and proliferating leucocytes than in differentiated leucocytes. In cells the protein was located mainly according to the marginal heterochromatin. We examined the signal intensity also in 5 Rett syndrome

patients with mutation in MECP2 but we didn't observe any difference compared to control. The cause of this is not clear; the role of X-inactivation, the possible binding of the antibody to the abnormal protein or the possibility that the abnormal cells are not able to proliferate came up as answers.

Table 2: Patients included in phenotype-genotype analysis

Case	Age (decimal year)	Mutation type	X-inactivation pattern	Phenotypic score
1	8,8	C880T (R294X)	NR	23
2	11,7	N		29
3	9,9	C316T (R106W)	R	32
4	12,3	C397T (R133C)	NI	22
5	11,7	N		24
6	12,8	C316T (R106W)	NR	11
7	6,0	C455G (P152R)	NR	17
8	7,6	C502T (R168X)	NR	31
9	8,2	C808T (R270X)	R	24
10	21,2	276insG	NR	27
11	8,8	N		15
12	11,5	1121del91;1322del9	R	31
13	13,5	N		21
14	12,5	N		18
15	12,5	N		31
16	8,3	C880T (R294X)	NI	19
17	8,1	C763T (R255X)	NR	16
18	4,7	C397T (R133C)	NR	17
19	9,3	1157del41	R	20
20	13,6	C808T (R270X)	NR	21
21	2,5	C473T (T158M)	NI	21
22	12,7	C880T (R294X)	NR	19
23	8,3	1160del7	R	25
24	18,6	T400C (S134P)	-	33
25	20,4	C473T (T158M)	NR	11
26	1,7	C608T (T203M)	-	23
27	16,9	C473T (T158M)	-	27
28	7,1	N		27
29	3,2	C502T (R168X)	NI	17
30	4,1	1163del35	NI	22
31	6,0	N		29
32	2,8	710delG	NI	24
33	5,8	C763T (R255X)	NR	19
34	4,6	C397T (R133C)	NI	11
35	2,9	806delG	-	18
36	3,6	C763T (R255X)	-	23
37	2,0	N		24

NR: non-random, R: random, NI: not informative, -: parents were not available. Patients at the age or bellow 6 years are bolded in blue. In the patients with no mutation in MECP2 (N) X-inactivation was not performed.

Table 3: Frequency of the not obligate but characteristic features of Rett syndrome in the different mutation groups (the characteristic signs for the given mutation group is in bold)

	Nonsense (%)	*Missense (%)*	*Deletion in exon 4 (%)*	*Normal (%)*	*Total (%)*
Average age (years)	8	10	6,5	9,5	8,5
Average of phenotypic score	21,7	20,4	23,3	22,5	22
Retarded psychomotor development before 6 month of age	4 (36)	6 (54)	**4 (67)**	**7 (78)**	21 (57)
Regression starts between 6-18 month of age	5 (45)	4 (36)	2 (33)	2 (22)	13 (35)
Microcephaly	**9 (89)**	8 (73)	4 (67)	6 (67)	27 (73)
Dystrophia	**6 (54)**	3 (27)	1 (16)	**5 (55)**	15 (41)
Small stature	2 (18)	**5 (45)**	1 (16)	**4 (44)**	12 (32)
Scoliosis	**7 (64)**	4 (36)	2 (33)	**6 (67)**	19 (51)
No hand use	5 (45)	3 (27)	**4 (67)**	2 (22)	14 (38)
Epilepsy	6 (54)	6 (54)	**5 (83)**	6 (67)	23 (62)
Irregular breath	8 (73)	6 (54)	**5 (83)**	2 (22)	21 (57)
Microcirculation abnormality	9 (89)	9 (89)	5 (83)	4 (44)	27 (73)
She doesn't say words	7 (64)	7 (64)	4 (67)	**9 (100)**	27 (73)
Sleeping problems	3 (27)	2 (18)	1 (16)	0 (0)	6 (16)
Severe motor retardation (she doesn't sit)	1 (9)	3 (27)	2 (33)	**6 (67)**	12 (32)
Start of walking is extremely retarded or she could never walk	4 (36)	5 (45)	**4 (67)**	**9 (100)**	22 (59)
Good non-verbal communication	9 (89)	8 (73)	4 (67)	7 (78)	28 (76)
Muscle tone abnormality	10 (91)	7 (64)	5 (83)	8 (89)	30 (81)
Joint contracture	9 (89)	9 (89)	5 (83)	6 (67)	29 (78)
Mood swing	6 (54)	3 (27)	**5 (83)**	**7 (78)**	21 (57)
In total	11	11	6	9	37 (100)

DISCUSSION AND SUMMARY

The genetic background of several diseases causing mental retardation is unknown, yet. The precise studies of those diseases where the mutations of gene or genes are discovered can help to reveal the rules of phenotype-genotype correlations.

Rett syndrome is such a disease the gene of which (methyl-CpG-binding protein 2, MECP2) was discovered in 1999. In the meantime more studies were published about the characteristics of the clinical picture, the mutations, role of X-inactivation and function of the protein.

We started with our prospective studies in 2001. Our aims were the following: 1. to perform detailed clinical evaluation (find those characteristics which are distinctive for Rett syndrome), 2. to determine the frequency of mutations in MECP2 in Hungarian patients, 3. to look for phenotype-genotype correlation, 4. to collect data about the patomechanism of the disease.

We answer these questions based on our studies (genetic analysis of 66 patients with the suspicion of Rett syndrome was performed):

1. **In our study we evaluated the usefulness of the phenotype scoring system (phenotype analysis was possible in 37 form 66 patients) which in our opinion can help to paediatricians and clinical geneticists to determine in which cases it is worth to ask for the mutation analysis of MECP2:**

- The anthropometric data (e.g. head circumference) of Rett syndrome patients are normal.
- **Some slight signs can predict the disease in infancy such as abnormal muscle tonus, tongue protrusion, abnormal eye and finger movements, hand stereotypes and tremor.**
- **The early sign of the disease is movement delay in infancy with apparently normal mental development until 1,5-2 years of age. It is characteristic that the speech development starts at 1 year of age then stops and regresses.**

- Characteristic features of the disease contain the loss of hand use but based on our observations we think that this skill is maintained on a level.
- **In most of the cases stereotype hand movement is not an early sign as it averagely appears at 3 years of age.**
- **The maintenance of the expression and understanding of feeling is an interesting feature regarding the very severe mental handicap.**
- **With the use of this phenotype scoring system (Table 1) acceptable hit probability (50-80%) can be achieved on mutation analysis of MECP2.**

2. **Until now we performed the mutation analysis of exon 2, 3and 4 of MECP2 in 66 cases, in 42 of them we found the clinical diagnosis of Rett syndrome possible, in 32 cases (76%) we detected a mutation. This result is similar to the data found in the literature (50-80%).**

In eight cases novel mutation was observed.

3a. X-inactivation studies were performed in 23 patients. **We found that in high percentage (49%) of Rett syndrome patients non-random (skewed) X-inactivation can be found.** This is in correlation with recent literature data. **In 91% the paternal X chromosome was inactivated** and regarding the knowledge that sporadic mutations are located mainly on the paternal X chromosome, it suggests the possible theory of cell selection published in the literature.

3b. **Phenotype-genotype analysis showed no direct correlation with mutation type and X-inactivation.** However, no direct correlation can be observed between clinical severity and mutation type some characteristics could be delineated. In some cases also X-inactivation may alter the clinical picture.

In the patients with the obvious clinical features of Rett syndrome but without mutation we found severely retarded motor development which suggests a distinct entity. The causative role of other genes yet unknown gives explanation for this. Lately mutations in exon 1 thought to be non-coding before was reported. In early epileptic forms mutations in cyclin-dependent kinase-like 5 (CDKL5) were demonstrated.

4. Our studies of the immune-fluorescent painting of MeCP2 reached only a preliminary state. **We found that on proliferating cells the signal intensity is higher than in differentiated cells. The signals were observed mainly according to the marginal heterochromatin.** We plan to carry out further immune-fluorescent and Western-blot studies to understand the role of the protein in the cells.

PUBLICATIONS AND PUBLISHED ABSTRACTS RELATED TO THE THESIS

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18-as trisomia-szindróma
21-es triszómia-szindróma
4p deléció-szindróma
5,10-metiléntetrahidrofolát reduktáz-hiány
5p deléció-szindróma
Argininosuccinát-lyase-hiány
Argininosuccinát-syntetase-hiány
Carbamyl phosphate syntetase-hiány
Cisztation B-szintáz hiány
Cystinuria
Galactokinase-hiány
Galactose-1-phosphate uridyltransferase-hiány
Hyperargininaemia
Homocisztinuria
Kobalamin-hiány

Mucolipidosis I.
Mucolipidosis II.
Mucolipidosis III.
Mucolipidosis IV.
Mucopolysaccharidosis I. H típus
Mucopolysaccharidosis I. H/S típus
Mucopolysaccharidosis I. S típus
Mucopolysaccharidosis II. típus
Mucopolysaccharidosis III. típus
Mucopolysaccharidosis IV. típus
Mucopolysaccharidosis II. típus
Mucopolysaccharidosis VI. típus
Mucopolysaccharidosis VII. típus
Mucopolysaccharidosisok
Ornitin transzkarbamiláz-hiány
Uridine diphosphate galactose-4-epimerase-hiány
Veleszületett fructose intolerancia
X-monosomia-szindróma
XXX-XXXX- és XXXXX-szindróma
XXXY- és XXXXY-szindróma
XXY-szindróma
XYY-szindróma

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1. *Kárteszi J.*, Morava É., Hermann R., Paschke E. és Kosztolányi Gy.: A Sanfilippo betegség klinikai és enzimszintű diagnosztikája (esetismertetés). A Magyar Gyermekgyógyász Társaság Dél-dunántúli Területi Szervezete Tudományos Ülése (Szigetvár, 2000. szeptember 23.)

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