Clinical Significance of Rare Copy Number Variations in Neurodevelopmental Disorders

PhD thesis

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1. Introduction

Neurodevelopmental disorders (NDDs) are chronic medical conditions characterized by deficits in one or more developmental domains due to altered neural development. NDDs include intellectual disability (ID), global developmental delay (GDD), autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), specific learning disorders, motor disorders, and communication disorders. Affected children face difficulties in adaptive functions, social interactions and self-care, which may translate to entire families under serious emotional (and often financial) stress. Early and accurate diagnosis is therefore not only important for optimal care of the affected child, but for alleviating the burden and guilt on the parents as well.

The etiology underlying NDDs is exceedingly complex, primarily including conditions that interfere with brain development and/or functioning. Genetic underpinnings show further heterogeneity. Some of the most common etiologic factors are copy number variations (CNVs), which are submicroscopic [a few dozen basepair (bp) to several megabase pair (Mb) large] structural variations in the genome. Disorders caused by CNVs tend to have variable expressivity, and many have been shown to have incomplete penetrance. Approximately 75% of CNVs occur as individually rare alterations, whereas the remaining 25% are recurrent rearrangements associated with repetitive elements in the genome [e.g. segmental duplications (SDs)]. SDs are highly homologous (at least 90% sequence identity) blocks of DNA that flank unique genomic segments, occur repeatedly in the genome, and are usually 10-400 Kb in size. High level of identity predisposes SDs to misalignment, and subsequent recombination may lead to the formation of reciprocal CNVs; a molecular mechanism referred to as non-allelic homologous recombination (NAHR).

The recommended gold standard techniques for diagnosing disease-causing CNVs (excluding clinically recognizable recurrent syndromes) are chromosomal microarray analyses (CMA). These methods allow genome-wide detection of CNVs at a high resolution with an estimated diagnostic yield of 15-20%.

2. Aims

The primary goal of my research was the systematic analysis of CMA results obtained from patients referred to the Tűzoltó street Unit of Semmelweis University's

Pediatric Center with NDDs and/or congenital anomalies in the ten-year period between 2011 and 2020. The aims of this study were the following:

1) To reevaluate clinically uncertain CNVs identified in the patients.
2) To determine the diagnostic yield of CMA in the cohort.
3) To delineate clinical features associated with definitive CMA results.
4) The genotype-phenotype association of patient subgroups carrying recurrent/functionally identical CNVs and comparison with the literature.
    a. Recurrent rearrangements of the short arm of chromosome 16.
    b. Overlapping microdeletions of the long arm of chromosome 14 including *SUPT16H* and *CHD8* genes.
5) The analysis and discussion of the genetic alterations identified in a phenotypic subgroup – patients with clinical features reminiscent of Silver-Russell syndrome.
6) To highlight potentially pathogenic variants of uncertain significance (VUS), and the dissemination of phenotypic data of all discovered VUS to facilitate genetic counselling in the future.

3. Methods

During the period between 2011 and 2020, 88 patients of the Tűzoltó street Unit of Semmelweis University's Pediatric Center underwent CMA testing. Children were selected for investigation if they had idiopathic DD/ID or a major congenital anomaly, and at least one additional suggestive feature (other NDDs, characteristic facies, multiple congenital anomalies, etc.), and the family consented to further genetic testing. At our Unit, the typical DiGeorge syndrome (proximal A-D 22q11.11 deletion encompassing *TBX1* gene), Williams syndrome and the deletion form of Prader-Willi syndrome are diagnosed by fluorescent *in situ* hybridization (FISH), therefore these cases are not included. 78 patients underwent CMA after negative routine cytogenetic evaluations, while 10 patients were tested to refine the findings of previous tests. These latter patients with microscopically visible rearrangements have been excluded from the cohort. Clinical data up to the point of genetic diagnosis/negative CMA result were retrospectively collected and organized.

Karyotypes (at standard band resolution of 450-550) were determined by analysis of 20 Giemsa-stained metaphases each from standard 72-hour peripheral blood lymphocyte cultures. Various platforms and analysis software were used for CMA; 50 patients (64.1%) were analyzed with platforms over 750K resolution, and only 5 patients (6.4%) with a relatively low 60K resolution. Relevant CNVs were validated using FISH or quantitative multiplex PCR of short fluorescent fragments (QMPSF) analysis. Parental studies were possible in 10 families using CMA, QMPSF or FISH.

Each VUS [and likely benign (LB) variant, if reported] was reevaluated according to the latest recommendations of the American College of Medical Genetics and Genomics (ACMG) as a primary guideline. In a first round of manual evaluation the following factors were taken into consideration: size, genes/other functionally important elements contained within the CNVs, and a search of case and control databases [Online Mendelian Inheritance in Man (OMIM), The Database of Genomic Variants (DGV), ClinVar, ClinGen, DECIPHER]. A second round of evaluation was performed with the help of the recently published SVInterpreter topologically associating domain-based tool. Finally, the CNVs were assigned to three groups for further study: 1) disease-causing variants, 2) VUS, and 3) benign variants. The main phenotypic features of the patients with disease-causing CNVs were compared to the patients with negative CMA results using the chi squared test. If any cell of the contingency table had an expected value less than five, the Fisher exact test was applied. Statistical analyses were performed using Microsoft Office 365 Excel.

4. Results

4.1. Overview

The final investigation cohort consisted of 78 individuals, 47 males and 31 females (male:female ratio 1.52:1). The average age at first clinical genetics consultation was 4.17 years (median 2.00 years, range from 4 days old to 20 years 7 months old). Inheritance was investigated in 12.8% of patients; including three families where only the mother agreed to testing (neither mother carried the CNV of the respective child). Samples were available from both parents for seven patients. These seven children carried in total 9 CNVs, three proved to be *de novo* alterations, three were maternally, and three were paternally inherited. As patients SEG2_26 and 27 are brothers, overall

we identified two carrier mothers and three carrier fathers. One of the carrier parents was healthy, while the other four showed mild symptoms (history of learning difficulties and/or pediatric obesity, behavioral disorders, etc).

The noteworthy results of my reevaluation efforts are listed in Table 1 (variants originally classified as LB and reclassified as B are not included).

Table 1. Results of reevaluation in the presented patient cohort

*All genomic locations are according to GRCh37.

LP: likely pathogenic, VUS: variant of uncertain significance, LB: likely benign

Patient	CNV*	Size (Kb)	Originial classification	Final classification
SEG2_49	14q11.2(21414942_21966929)x1	552.0	VUS (LP)	P
SEG2_68	14q11.2(21438704_22101647)x1	662.9	VUS (LP)	P
SEG2_89	14q11.2(21511829_22131455)x1	619.6	VUS (LP)	P
SEG2_61	Xp22.33(566719_807207)x3	240.5	VUS (LP)	P
SEG2_32	16p12.2(21953152_22480514)x3	527.4	VUS	LP
SEG2_20	2q37(242855645_243028377)x1	172.7	VUS	LB
SEG2_53	2q37(242855645_243030854)x1	175.2	VUS	LB
SEG2_65	2q37(242855645_243033605)x1	177.9	VUS	LB
SEG2_47	17p11.2(18933772_19128870)x1	195.1	VUS	LB
SEG2_42	17q12(34437475_34475514)x4	38.0	VUS (LB)	LB
SEG2_81	Yq11.221(15421662_ 15734785)x2	313.1	VUS (LB)	LB

4.2. Disease-causing variants

Disease-causing variants (n=30) were identified in 29 patients (15 males and 14 females; one girl carried two P variants), which translates to an overall diagnostic yield of 37.18%. The disease-causing CNVs were on average 3.481 Mb large (median 1.124 Mb); 19/30 were deletions and 11/30 were duplications. Chromosome 16 was most frequently affected (9/30; 30.0%; note: as the sample size is small, percentages are meant to enhance comparability), followed by chromosome 22 (4/30; 13.3%), and chromosomes 14, 17 and X (3/30; 10.0% each).

Information regarding the disease-causing CNVs is detailed in Table 2.

Table 2. Disease-causing CNVs identified in the presented patient group

Kb: kilobase; *: GRCh38; other genomic coordinates according to GRCh37

Patient	Copy Number Variation	Size (Kb)
SEG2_5	16p13.3(3263725_4309863)x1*	1046.1
SEG2_7	22q11.21q11.22(21934268_22336871)x3	402.6
SEG2_12	22q13.33(50971316_51224252)x3	252.9
SEG2_15	19p13.3(753219_1477508)x3	724.3
SEG2_17	16p11.2(29620689_30190568)x3	569.9
SEG2_21	18q22.1q23(69071896_80256240)x1*	11184.3
SEG2_26	16p11.2(29624765_30199351)x3	574.6
SEG2_27	16p11.2(29624765_30199351)x3	574.6
SEG2_30	17p13.3(7_2084490)x1	2084.5
SEG2_32	16p12.2(21953152_22480514)x3	527.4
SEG2_33	15q11.2q13.1(22765628_29060493)x1	6294.9
SEG2_37	16q22.2q23.3(72155844_82148404)x1	9992.6
SEG2_39	16p11.2(29656684_30190568)x1	533.9
SEG2_44	2q23.1(149060704_149313819)x3	253.1
SEG2_49	14q11.2(21414942_21966929)x1	552.0
SEG2_50	8p23.1(7117851_11969155)x1	4851.3
SEG2_52	1p36.33p36.22(820001_9348000)x1	8528.0
SEG2_53	16p11.2(28824802_29040571)x1	215.8
SEG2_59	17p11.2(16727490_20433502)x1	3706.0
SEG2_61	Xp22.33(566719_807207)x3	240.5
SEG2_62	Xp22.31(6537108_8167604)x0; 14q11.2q32.33(20052038_106871264)hmz	1630.5 86819.2
SEG2_68	14q11.2(21438704_22101647)x1	662.9
SEG2_70	4q32.2q35.2(161869551_190790881)x1	28921.3
SEG2_78	Xq22.1q23(101597527_111626047)x1*	10028.5
SEG2_80	22q11.21q11.22(21460640_22962962)x1	1502.3
SEG2_82	19q13.43(57243585_58445449)x3*; 22q13.33(49368551_50759338)x1*	1201.9 1390.8
SEG2_85	16q12.2q21(56340118_60294492)x1	3954.4
SEG2_87	17q12(34835983_36243365)x3	1407.4
SEG2_89	14q11.2(21511829_22131455)x1	619.6

4.3. Phenotypic comparison

We compared the main phenotypic features of the disease-causing CNV carrier patients and the negative CMA group. Due to the patient selection criteria, NDDs were common in both groups, as were congenital anomalies of the internal organs. Postnatal growth delay was the only symptom to approach significance (p=0.05564). Pectus excavatum (p=0.07484), brain imaging abnormalities (p=0.07848), global DD

(0.08070), the sub-phenotype of speech and language delay (p=0.08070) and macrocephaly (p=0.08919) were more commonly, but non-significantly associated with disease-causing CNVs. Conversely, errors of refraction were more common in the negative group, the difference reached significance (p=0.02880).

4.4 Recurrent CNVs of the short arm of chromosome 16

Chromosome 16p has a high percentage of SDs, predisposing it to NAHR, and therefore recurrent rearrangements. Six of the nine chromosome 16 CNVs corresponded to recurrent microdeletion/microduplication regions on the short arm (Figure 1).

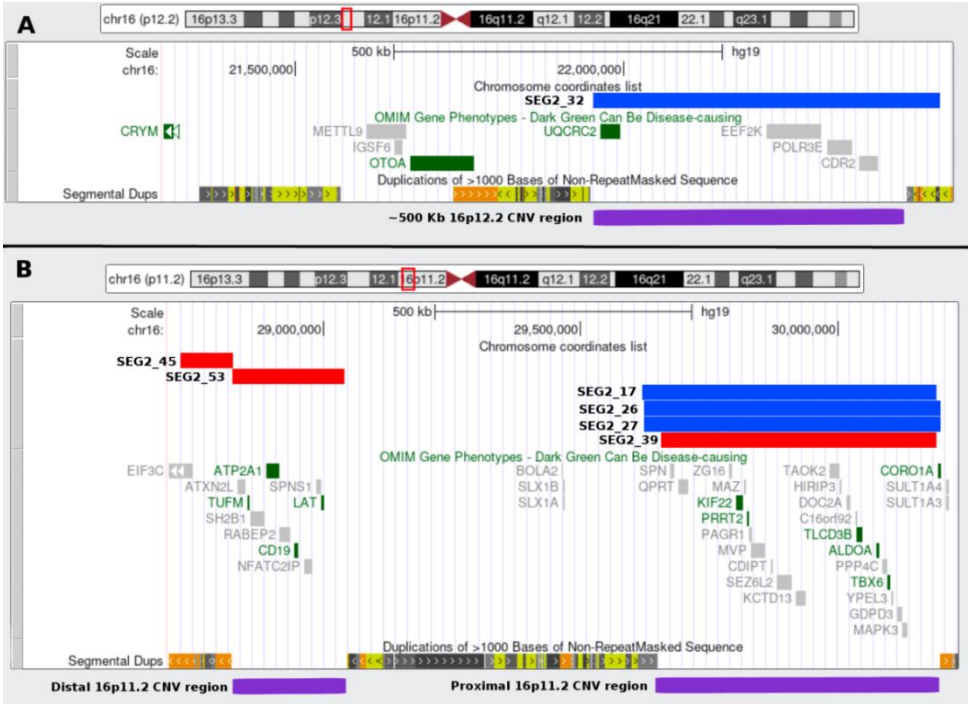

Figure 1. Recurrent copy number variations of the short arm of chromosome 16 and the rearrangements of the presented patients

A: Region 16p12.2. **B**: Recurrent CNV regions in 16p11.2. The purple bars denote the known recurrent CNV regions; red bars indicate deletions, blue bars indicate duplications identified in the patients. Disease-causing OMIM genes are in dark green.

One patient (SEG2_32) had a gain reciprocal to the NDD predisposition 16p12.2 deletion, bolstering the duplication's similar, but contentious predisposing effect. Another patient (SEG2_53) had the typical distal 16p11.2 deletion associated with NDDs and obesity. One child lacking the typical phenotype (SEG2_45) carried a non-

pathogenic CNV located directly upstream of the recurrent region, consolidating the distal 16p11.2 region's role in disease pathogenesis. Amongst the 16p alterations, a noteworthy four were gains or losses of the proximal 16p11.2 region, which corresponds to 5.1% of the entire cohort, and 13.8% of children diagnosed (SEG2_17, 26, 27 and 39). Phenotypes align with scientific literature.

4.5. Microdeletions of 14q11.2 involving SUPT16H and CHD8 genes

Microdeletions of one non-recurrent region - chromosome region 14q11.2 encompassing *CHD8* and *SUPT16H* genes - were enriched in our study. *CHD8* is an estabilised ASD driver gene, and is associated with an autism sub-phenotype including macrocephaly. *SUPT16H* has recently been linked to NDDs. Three of 78 patients (3.8% of the studied cohort, 10.3% of diagnosed patients, SEG2_49, 68 and 89) carried approximately 500 Kb large deletions of 14q11.2 (Figure 2).

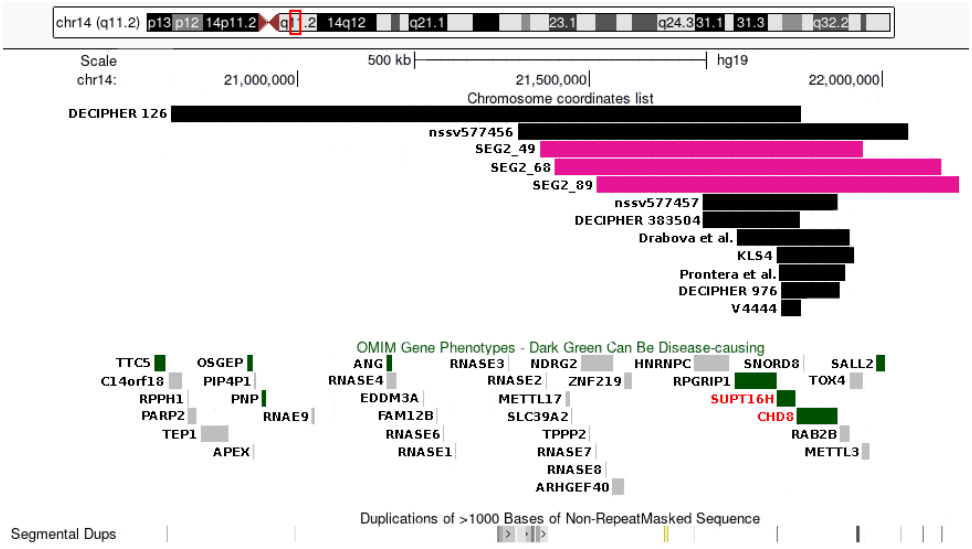

Figure 2. Microdeletions of chromosome 14q11.2

Pink bars denote the presented patients, black bars represent patients from the literature/databases.

The microdeletion is associated with NDDs, macrocephaly and characteristic facial features. I compared the presented patients' phenotypes to those accessible from the literature and online databases, which enabled further phenotypic expansion: growth delay/short stature, muscular hypertonia/spasticity and ventriculomegaly are all novel associated features noted in 2/3 patients in the current study. Only 40% of patients were

reported to have macrocephaly (neither of the three current patients had increased head circumference). Overall these results highlight the fact that macrocephaly is not an obligatory symptom in SUPT16H-CHD8 microdeletions.

4.6. CMA results in patients with phenotypic features reminiscent of Silver-Russell syndrome

Silver-Russell syndrome (SRS) is an imprinting disorder that causes pre- and postnatal growth failure. SRS is primarily a clinical diagnosis: the Netchine-Harbinson Clinical Scoring System (NH-CSS) is the current gold-standard scoring system used to obtain a clinical diagnosis of SRS. Molecular testing enables confirmation of the clinical diagnosis in approximately 60% of cases. The classical form of SRS is caused by hypomethylation of the H19/IGF2 intergenic differentially methylated region, or other genetic defects of the 11p15.5 region. Other molecular causes that have been identified in patients with a clinical SRS diagnosis, or should be considered in the differential diagnosis, include maternal uniparental disomy (UPD) of chromosomes 7, 20, 16 and 14, and several pathogenic CNVs.

Two patients in the discussed cohort, who presented with phenotypes reminiscent of Silver-Russell syndrome, underwent CMA after negative testing of SRS-regions on chromosomes 7 and 11. For patient SEG2_62, CMA identified a large loss of heterozygosity (LOH) on chromosome 14 (20052038_106871264 Mb; GRCh37) (Table 2). This finding was followed up by methylation analysis and maternal UPD 14 (Temple syndrome) was confirmed. For patient SEG2_37, CMA revealed a 10 Mb large deletion of chromosome 16: arr[GRCh37]16q22.2q23.3(72155844_82148404)x1 (Tables 2 and 3). Analysis of this child and comparison with literature data and cases listed in online databases established the differential diagnostic importance of 16q22.2q23.3 deletions in regards to SRS-like patients.

An additional SRS-like patient (identified as 2021.1), though not a part of the original cohort, is discussed due to the finding's relevance. CMA revealed a 77 kb deletion: arr[GRCh37]8q12.1(57079399_57155945)x1 (Table 3); *de-novo* occurrence was proven by quantitative PCR of the parental DNA samples. The child's deletion affects *PLAG1* gene, which has been implicated in SRS recently through both pathogenic point mutations and chromosome 8q12.1 CNVs. In comparison to the

currently reported cases carrying *PLAG1* deletions, the presented patient exhibited the smallest deletion, unequivocally confirming *PLAG1* as a SRS-causing gene.

Table 3. Patients with SRS-like phenotype and their causative CNVs

Genomic coordinates accoring to GRCh37. SGA: small for gestational age, IUGR: intrauterine growth restriction, NH-CSS: Netchine-Harbinson Clinical Scoring System, JH: joint hypermobility, CALM: café au lait macule

	SEG2_37	**Patient 2021.1**
CNV	16q22.2q23.3(72155844_82148404)x1	8q12.1(57079399_57155945)x1
Size	9.992 Mb	77 Kb
Candidate gene(s)	*WWOX, MAF*	*PLAG1*
SGA	no	no (*but IUGR*)
Relative macrocephaly at birth	yes	yes (*later microcephaly*)
Postnatal growth delay	yes	no
Feeding difficulties	yes	yes
Protruding forehead	yes	yes
Body asymmetry	no	no
NH-CSS	**4/6**	**3/6**
DD/ID	yes	no
Other	triangular face, JH, CALMs, delayed eruption of teeth, ear abnormality	triangular face, complicated perinatal adaptation

4.7. Variants of unknown significance

We identified 24 VUS in 17 children (21.79% of the cohort); five individuals carried two, while one individual carried three VUS simultaneously. Four children carried VUS in addition to disease-causing variants. The average size of the VUS variants was 585.9 Kb (median 228.2 Kb), 12 were losses and 12 were copy number gains.

4.7.1. Patients with potentially pathogenic VUS

Patient SEG2_81 has a 154 Kb large chromosome 20 duplication (arr[GRCh37]20p11.21(24554628_24708699)x3) encompassing *SYNDIG1* gene. The 5-year-old boy presented with moderate global developmental delay. His speech delay is

particularly severe as he has no spoken words. Preliminary neuropsychiatric opinion states that the patient has a complex NDD affecting the quality of many neurodevelopmental domains, including social interactions, behavior, and processing functions. Patient SEG2_81's 20p11.21 duplication was inherited from the father. *SYNDIG1* is a brain-specific transmembrane protein proven to be a regulator of excitatory synapse development in rat brain. *SYNDIG1*-deficient excitatory synapses have impaired structure and function, suggesting an important role in normal synapse development. No comparable duplications of *SYNDIG1* have been reported in the literature or online databases. Nevertheless, the currently suspected pathogenesis of patient SEG2_81's phenotype implicates faulty synaptic development.

Patient SEG2_57 is a young boy with severe DD/ID, behavioral stereotypies and multiple congenital anomalies (bilateral talipes equinovarus, bilateral complete syndactyly of the fingers and the toes, nail dystrophy, macrocephaly and postnatal overgrowth, craniofacial minor anomalies, spasticity, mild congenital heart disease, strabismus). The etiology of the child's phenotype is complicated by the possibility of perinatal hypoxia and post-operative sudden loss of vision, multiple symptomatic focal epileptic attacks and diffuse hypoxic-ischaemic encephalopathy. Extensive genetic examinations (including G-banding, CMA, WES and mitochondrial genome analysis) revealed three VUS upon CMA testing. Noteworthy is the 384 Kb large chromosome 4 duplication containing *PPP3CA* gene: (arr[GRCh37]4q24(102058416_102443207)x3). The phenotype of the presented SEG2_57 patient overlaps with disorders associated with *PPP3CA* (loss-of function variants: moderate/severe DD/ID, autistic behavior, generalized muscular hypotonia or spasticity, talipes equinovarus, cortical vision loss, cerebral atrophy; and gain-of-function variants: arthrogryposis, ID, generalized seizures and behavioral stereotypies). The duplication of this gene plausibly contributed to the patient's complex disorder, genotype-phenotype correlation is however greatly confounded by the presence of multiple uncertain environmental factors. The syndromic origins of the child's epilepsy and vision loss are questionable, but they might be attributable to decompensation of an existing genetic disorder. The complete syndactyly affecting all four extremities remains unexplained, which seems counter-intuitive at first glance, however, approximately 60% of syndactyly cases are sporadic, and hereditary cases are often isolated and multifactorial.

5. Conclusions

In this study I have systematically analyzed the CMA results of NDD patients presenting at our Unit's Genetic Counseling out-patient clinic between 2011 and 2020. I have made the following observations and have come to the subsequent conclusions.

1) The scientific community recommends reevaluation of VUS every 2-3 years. I have conducted reevaluation of the CNVs identified in the presented patients according to the most recent ACMG guidelines. **My work has enabled the reclassification of VUS in eleven patients, five of whom can now be considered carriers of clinically significant variants.** Despite these efforts, the results of 13/78 patients (16.67%) remain clinically uncertain.

2) **The diagnostic yield in the presented patient cohort was determined to be 37.18%.** Early estimates of CMA yield (15-20%) were based on studies with very large cohorts and broad selection criteria, using lower resolution array platforms. The diagnostic yield of this study is comparable to publications with similarly small cohorts tested with higher resolution platforms.

3) Although the small sample size limits statistical analyses, **the following clinical features increased the probability of identifying a disease-causing CNV in the presented patients: postnatal growth delay, brain imaging abnormalities, global DD, macrocephaly and pectus excavatum.** The first three corroborate literature data. Interestingly, in this cohort macrocephaly - and not microcephaly – emerges as a phenotypic clue. This is most likely due to the small sample size and possibly sampling bias; i.e. patients with obvious microcephaly are often sent to clinical genetics consultations, and are therefore "overrepresented" in the entire cohort, similarly to ID. **This result corroborates the need for CMA in children who have macrocephaly but lack symptoms of a specific overgrowth syndrome or skeletal dysplasia.**

4) The presented cohort enables discussion of recurrent CNVs on the short arm of chromosome 16 and microdeletions of the long arm of chromosome 14 as well.

a. A **duplication reciprocal to the ~500 Kb large NDD predisposition region on 16p12.2** has been identified in patient SEG2_32. The duplication has conflicting classifications in the scientific literature and online databases. **I argue for its consideration as an NDD risk factor similar to the reciprocal deletion**,

corroborated by SEG2_32's case. One patient, SEG2_53 has been identified as a carrier of the distal recurrent 16p11.2 deletion (~220 Kb, encompassing *SH2B1*), and she presents the expected phenotype. Patient SEG2_45 carries a deletion directly adjacent to the recurrent region, further implicating it as pathogenic, as he lacks the typical phenotype. **This result suggests that the upstream region does not convey similar phenotypic consequences through position effects.** Four of the presented patients have been revealed as carriers of the proximal recurrent 16p11.2 (~600 Kb) alterations. Patients SEG2_26 and SEG2_27 inherited their duplication from their mother, who was only mildly effected, if at all. The brothers themselves presented with varying severity, showcasing the **interfamilial variable expressivity linked to recurrent rearrangements.**

b. Three patients were shown to be carriers of overlapping **microdeletions of 14q11.2 encompassing *CHD8* and *SUPT16H* genes**. These children allowed **delineation of several new phenotypic features associated with the deletion, inlcuding somatic DD/short stature, muscular hypertonia/spasticity and ventriculomegaly. Importantly, macrocephaly should no longer be considered a cardinal feature of the microdeletion.**

5) The analyzed patients also allowed for ascertainment of a phenotypic subgroup, namely patients with characteristics resembling Silver-Russell syndrome. The presented patients showcase the molecular heterogeneity associated with SRS. Two patients carried pathogenic CNVs. **The 16q22.2q23.3 deletion in patient SEG2_37 is a novel SRS-like disorder.** In recent years, variants of *PLAG1* gene have been emerging as SRS-disease-causing. **The pathogenicity of the gene and 8q12.2 deletions is confirmed** through patient 2021.1.

6) Lack of scientific knowledge confounds classification of VUS, which represent a great difficulty in everyday genetic counselling. To facilitate future reclassification endeavours, I have presented detailed phenotypic and scientific data regarding the VUS identified in the presented patients. **I discuss in detail two novel variants containing genes possibly relevant for the associated phenotypes**: SNVs in ***PPP3CA* gene** have been associated with two complex disorders, both of which show partial overlap with patient SEG2_57's phenotype; and ***SYNDIG1***, a gene implicated in faulty synaptic development, duplicated in patient SEG2_81 with a complex NDD.

10. Author's publications

10.1. Publications related to the dissertation

- **Lengyel A**, Pinti É, Pikó H, Jávorszky E, David D, Tihanyi M, Gönczi É, Kiss E, Tóth Z, Tory K, Fekete G, Haltrich I. (2020) Clinical and genetic findings in Hungarian pediatric patients carrying chromosome 16p copy number variants and a review of the literature. Eur J Med Genet, 63(10): 104027. https://doi.org/10.1016/j.ejmg.2020.104027
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- Baba N, **Lengyel A**, Pinti E, Yapici E, Schreyer I, Liehr T, Fekete G, Eggermann T. (2022) Microdeletions in 1q21 and 8q12.1 depict two additional molecular subgroups of Silver-Russell syndrome like phenotypes. Mol Cytogenet, 15(1): 19. https://doi.org/10.1186/s13039-022-00596-z
  IF: 1,904
- **Lengyel A**, Pinti E, Pikó H, Árvai K, Abonyi T, Némethi Z, Fekete G, Haltrich I. (2022) Clinical evaluation of rare copy number variations identified by chromosomal microarray in a Hungarian neurodevelopmental disorder patient cohort. Mol Cytogenet, 15(47). https://doi.org/10.1186/s13039-022-00623-z
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10.2. Other publications

- **Lengyel A**, Pinti É, Bertalan R, Bajnóczky K, Tóth Zs, Kiss E, Fekete Gy, Haltrich I. (2018) Barangolás egy ritka betegség világában: a cri du chat szindróma. Gyermekgyógyászat, 69(2): 113-118.
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  IF: 0,564

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- Pinti E, **Lengyel A**, Fekete G, Haltrich I. (2018) A nemi identitás és fejlődés zavarainak genetikai háttere. GYERMEKORVOS TOVÁBBKÉPZÉS, 17(3): 134–137.
- Pinti E, **Lengyel A**, Sallai Á, Fekete G, Haltrich I. (2018) Nemi kromoszóma-rendellenességek vizsgálata gyermekkorban [Examination of sex chromosome abnormalities in childhood]. Orv Hetil, 159(27): 1121-1128. https://doi.org/10.1556/650.2018.31081
  IF: 0,564
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