

Psychopathology in mothers of children with pathogenic Copy Number Variants

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Abstract (200 words)

Background: Caring for children with pathogenic neurodevelopmental Copy Number Variants (CNVs) (i.e., deletions and duplications of genetic material) can place a considerable burden on parents, and their quality of life. Our study is the first to examine the frequency of psychiatric diagnoses in mothers of children with CNVs compared to the frequency of psychiatric problems in age-matched mothers from a large community study.

Methods: Case-control study. 268 mothers of children with a CNV diagnosed in a medical genetics clinic and 2,680 age-matched mothers taking part in the ALSPAC study.

Results: Mothers of children with CNVs reported higher frequency of depression, anorexia, bulimia, alcohol abuse and drug addiction problems compared to the age-matched mothers from the community sample. Focusing on psychiatric problems arising immediately after the birth of the index child, the levels of depression symptoms were similar between the two groups (48% in mothers of children with CNVs vs. 44% in mothers of the community sample, $p=0.43$), but mothers of children with CNVs had higher frequency of anxiety symptoms (55%) compared to mothers from the community sample (30%, $p=0.03$).

Conclusion: Our study highlights the need for health-care providers to devise treatment plans that not only focus on meeting the child's needs, but also assessing and if needed, addressing the mental health needs of the parent.

Keywords: psychiatric disorders, maternal psychopathology, mothers, Copy Number Variants,

Key messages

What is already known on this topic

Caring for children with complex presentations of neurodevelopmental and physical health problems can be taxing for the mothers. High levels of emotional distress have previously been reported for mothers of children with developmental disabilities. An increasing number of children is now diagnosed with sub-microscopic pathogenic Copy Number Variants (CNVs), which increase risk of a range of mental health conditions. There is however a paucity of research evaluating the mental health of the mothers of these children.

What this study adds

Our study is the first to compare the frequencies of mental health symptoms in mothers of children with pathogenic CNVs and age-matched mothers from a large community study. We find that the mothers of children with pathogenic CNVs report more psychiatric problems

How this study might affect research, practice or policy

Our findings highlight the need for the monitoring of the mental health problems of these parents as well as, if indicated, the provision of psychiatric support.

Introduction

Recent advances in genetic technologies have led to the detection of sub-microscopic deletions or duplications of chromosomal regions, otherwise known as Copy Number Variants (CNVs). Certain relatively rare Copy Number Variants (CNVs) have been shown to increase the risk for a number of neurodevelopmental and psychiatric conditions, including Attention Deficit Hyperactivity Disorder, Autism Spectrum disorder and anxiety disorder [1 2] as well as other health problems. [3]

The multitude of physical and mental health comorbidities associated with pathogenic CNVs in children can place a considerable burden on parental caregiving. [4] For example, there is evidence that caring for a child with developmental disorder can be taxing on the parent in terms of their emotional (e.g., [5]) and physical well-being (e.g., [6]). Research has indicated that mothers with a child with a developmental disability were more likely to experience difficulties coping with stress [7] and reported worse emotional well-being relative to females from the general population. [8] Moreover, mothers with these problems were more likely to have children who had more behavioural problems (e.g.,[9]).

Taking into account the ‘diagnostic odyssey’ that parents of children with CNVs often have to go through [10], which in turn can impact their quality of life [11], as well as the burden of caregiving on the parents placed by the multitude of physical and health comorbidities associated with pathogenic CNVs, there is paucity of research to examine the frequency of psychiatric problems in the parents of children with CNVs. Previous research has indicated high emotional distress in parents of children with CNV. [4] However, our study is the first to examine the frequency of psychiatric symptoms in mothers of children with CNVs in comparison with age-matched mothers from a large community study. We hypothesized that mothers of children with CNVs have more psychiatric symptoms compared to mothers from the general population. Finally, studies of adults with pathogenic CNVs are indicating they are at a higher risk of psychiatric problems, including internalizing disorder[12 13]. We therefore hypothesized that mothers of children with CNVs who are also carriers of CNVs themselves, would experience more depression and anxiety, compared to mothers without these CNVs.

Methods

Samples

Mothers of children with CNV

Recruitment of the children with CNV was performed through 14 genetics clinics across the UK and the charities Max Appeal, Unique and the 22Crew, as well as social media and word of mouth.

Children's CNV genotypes were established from medical records as well as in-house genotyping at the Cardiff University MRC Centre for Neuropsychiatric Genetics and Genomics using microarray analysis. Considering our overarching goal of examining the psychopathology of mothers of children with CNVs, we considered it appropriate to also include all children who took part in face-to-face assessments in these studies, meaning that a variety of CNVs was represented. Variants were included if a) pathogenic or likely pathogenic variants according to the American College of Medical Genetics and Genomics guidelines [14], and/or b) were associated with neurodevelopmental outcomes [15].

272 mothers with children with a CNV (mean age 41.2 years (SD=9.8) at the time of assessment and mean age 30.3 years (SD=7.0) when their child was born) were recruited from the Experiences of people with Copy number variants study (ECHO) (see: <https://www.cardiff.ac.uk/mrc-centre-neuropsychiatric-genetics-genomics/research/themes/developmental-psychiatry/echo-study-cnv-research>), and the IMAGINE-ID study (<http://www.imagine-id.org/>). For a list of the children's CNVs see Supplementary table 1.

For 33% of our sample (N=89) we also had information from the parents on whether the CNV was de novo or was inherited. 10% of the mothers (N=9/89) were CNV carriers.

Our study was approved by the National Health Service Wales Research and NHS London Queen Square research ethics committees. Parents provided informed written consent for their participation.

Mothers of children from a community sample

2,680 mothers, matched for their age and the age of their child to the mothers of children with CNV sample, were recruited from the Avon Longitudinal Study of Parents and Children

(ALSPAC). ALSPAC (<http://www.bristol.ac.uk/alspac/>) is an ongoing population-based cohort which started with inviting pregnant women resident in Avon in the southwest of England, with expected dates of delivery 1st April 1991 to 31st December 1992 to take part in the study. The initial number of pregnancies enrolled was 14,541 (for these at least one questionnaire has been returned or a “Children in Focus” clinic had been attended by 19/07/99). These initial pregnancies resulted in a total of 14,676 fetuses, leading to 14,062 live births with 13,988 children who were alive at 1 year of age. [16 17]

Ethical approval was provided by the Local Research Ethics Committees and the ALSPAC’s Law and Ethics Committee. Parents provided informed written consent and were allowed to withdraw at any time.

Measures

Mothers of children with CNV

Psychopathology in the mothers of children with CNVs was assessed using the Parental Psychopathology section of the parent version of the Child and Adolescent Psychiatric Assessment (CAPA). [18] The CAPA is a semi-structured interview that generates categorical diagnoses as well as symptom counts of childhood psychopathology. The parental psychopathology section includes questions about a parent’s own psychopathology. Stem questions enquire about whether the parent has ever had depression, anxiety, panic, eating disorder, Obsessive Compulsive Disorder (OCD), psychosis, or problems with alcohol or drugs. If the parent answered ‘yes’ to any of these questions, subsequent questions were asked enquiring about the onset and the severity of the problem (i.e., whether the subject sought treatment, received medication, or was hospitalized). Information regarding onset was only coded by the rater if the parent could report an exact year of onset, therefore, age at onset data were missing in some instances. For more details see:

<https://devepi.duhs.duke.edu/measures/the-child-and-adolescent-psychiatric-assessment-cap/>.

Mothers from community sample

Various questionnaires were administered to mothers at different time points of their child’s development. To enable comparisons with the ECHO study, we selected questions included in the questionnaires that 1) were phrased either identically or as close as possible to the questions

asked in the CNV study and 2) were administered when the children and the mothers in the ALSPAC study were within a similar age range to the children and the mothers of the CNV study, in order to facilitate matching (see Data Analysis below). For these reasons, we selected the mental health related questions that were included in the ‘Mother and family’ questionnaire (Section A – standard ALSPAC health related questions -link to the questionnaire: <http://www.bristol.ac.uk/media-library/sites/alspac/migrated/documents/ques-m13-mother-and-family.pdf>) that was administered to mothers when their child was 8 years old, as the mean age of the mothers and the children was similar to the mean age of the mothers and children in the ECHO study. An example of the format of the questions is as follows: Have you ever had any of the following problems: bulimia (‘yes, had it recently’ (‘in past year’)/ ‘yes, in past, not recently’/ ‘no never’). The problems we included in our study were: severe depression, bulimia, anorexia, alcohol abuse, and drug addiction and anxiety. We considered as a ‘yes’, either ‘yes recently’, or ‘yes’ in the past’ answers. Taking into account that in the CNV study the questions about depression included treatment and hospitalization, we compared this question with the question ‘Have you ever had severe depression’ which was included in the above questionnaire that was administered to mothers when their child was 11 years old.

Data analysis

We ran descriptive statistics using R version 3.6.0. To compare the frequency of psychiatric problems between both samples, we matched the mothers based on their current age using the R ‘MatchIt’ package, with a proportion 1 (genetic sample) to 10 (community sample). We then compared the frequencies of each group using chi-squared tests.

Results

Psychiatric problems in mothers of children with CNV

The socio-demographic characteristics of the mothers of children with CNV are described in Table 1. Depression was the most common psychiatric problem, affecting 54% (N=146), of the sample (Table 2). Out of those, the majority sought treatment (84%, 121/144), and received medication (74%, 108/145), while 1% (13/132) was hospitalized. Of the 146 mothers reporting depressive symptoms, 88 indicated the onset, and of those 43/88 (49%) reported their depressive symptoms started after the birth of their child with a CNV. Anxiety symptoms were reported by 31% (N=85), of the sample. Similar to depression, the majority of individuals sought treatment (73%, 61/83), and 55% (46/84) received medication for their anxiety, while 4% (3/84) was hospitalized. Of the 85 mothers who reported anxiety symptoms, 49 indicated the onset and of those 55% (27/49) reported their anxiety started after the birth of their child. Other psychiatric symptoms reported included panics (29%), phobias (21%), anorexia and bulimia (12%), other problems (i.e., psychotic or OCD related disorders) (13%), and alcohol/drug problems (6%). We found no evidence that the frequency of depressive symptoms ($\chi^2=0.77$, $p=0.38$) or anxiety ($\chi^2=0.01$, $p=0.92$) was higher in mothers who also carried a CNV themselves ($n=9$), compared to mothers who did not ($n=80$) (Table 3).

Comparisons between mothers of children with CNV and community mothers

We did not have data on age for 5 mothers of children with CNV, therefore, our comparison of the frequency of depressive symptoms was based on 268 mothers of children with CNV and 2,680 age-matched community mothers. Because the question in the community sample did not correspond exactly to the question completed by the mothers of children with CNVs (see Methods), we compared the frequency of depressive symptoms in this group, with all three levels of the depression-related question in the mothers of children with CNV sample (Table 3). Mothers of children with CNV had higher frequency of all the three levels of depressive symptoms compared to mothers from the community ($p<0.001$). Furthermore, mothers of children with CNV reported higher frequency of anorexia, bulimia, alcohol abuse and drug addiction symptoms, compared to mothers from the community sample.

The frequency of depressive symptoms arising post the birth of the index child was similar between mothers of children with CNV (48%) and mothers from the community sample (44%, $p=0.43$). There was however evidence of a difference in the frequency of anxiety symptoms arising post the birth of the index child (55% mothers of children with CNV vs. 30% mothers from the community sample, $p=0.03$).

Discussion

Our study is the first to compare the frequency of psychiatric problems between mothers of children with CNVs and an aged-matched sample of mothers from a community study. The findings supported our hypothesis. Psychiatric problems including depression, eating disorders, and substance abuse/ addiction, were more frequently reported by the mothers of children with CNVs, compared to mothers from the community sample. Studies in the general population (e.g., [19], as well as in 22q11.2 Deletion Syndrome [20], have indicated associations between parental and child psychopathology. However, the nature and direction of these associations is not yet clear. For example, it is possible that maternal psychiatric problems may increase the risk of psychiatric problems in the child via shared genetic background or via the family environment. Studies on 22q11.2 Deletion syndrome (22q11.2DS), a pathogenic CNV associated with a 25-fold increased risk for schizophrenia, have indicated that environmental factors are related to the child's mental health difficulties (e.g., [21 22]). For example, a study by [22] found that better parental organisation was associated with fewer difficulties in children with 22q11.2DS. Maternal psychiatric problems may contribute to a less structured family environment that could in turn increase risk of psychiatric problems in the child. On the other hand, it is also possible that the increased physical and mental health problems associated with the CNV in the child may increase the risk of depression and anxiety in the parent due to the high demands on parental caregiving. Longitudinal studies in families of children with developmental disabilities have indicated bi-directional relationships between parenting stress and child behaviour problems. [23] Futures studies are needed to examine the relationship between parental psychopathology, family environment and child psychopathology in families of children with CNVs, cross-sectionally as well as longitudinally.

We did not find differences in the frequency of depressive and anxiety symptoms between mothers who were CNV carriers themselves compared to mothers who were not. This result is likely due to low power given the small sample sizes. Future studies are needed to better understand how maternal psychopathology may be related to child psychopathology in the context of pathogenic CNVs.

Anxiety symptoms were more frequently reported by mothers of children with CNV after the birth of their child with a CNV, compared to mothers from the community sample.

Our study highlights the need for the monitoring and early intervention for mental health symptoms as well as the effective management of established conditions, not only in the children with neurodevelopmental risk CNVs, but also their mothers. Indeed, our findings are in line with studies providing evidence that bringing up a child with a neurodevelopmental disorder can be taxing on the parent in terms of their emotional (e.g., [5]) and physical well-being (e.g., [6]). Research has identified that mothers with a child with a developmental disability were more likely to experience difficulties with coping with stress [7], as well as worse emotional well-being than women from the general population. [8 9]

Our study has some limitations. There are ascertainment differences across the studies (mothers of children with CNV were recently recruited because of their child's genetic diagnosis, whereas ALSPAC mothers were originally recruited because they were pregnant and invited to take part in a birth cohort study). Also, the fact that children with CNVs were recruited from genetics clinics might indicate that they were enriched for more severe cases and parental distress and as such the rates of psychopathology may not be representative of the general population. Furthermore, there were also differences in the psychiatric assessment measures used in the two groups and it was not possible to validate the questions asked in the community sample in the CNV sample or vice versa. It is therefore possible that we are over- or underreporting the differences between the two samples. Additionally, age of onset was not available for approximately 40% mothers of children with CNVs who reported depressive or anxiety symptoms. We do not know whether and how this relatively high non-response rate may have affected findings. Another limitation is that we did not examine whether and how the children's psychopathology may influence their mothers. Future studies are needed to replicate and expand our results. Finally, given the age range of our samples, new incidences of depression are likely to occur. Thus, our study is likely to under-estimate the overall frequency of depression in both samples.

In conclusion, we found higher frequencies of depressive symptoms and a number of other psychiatric problems in the mothers of children with CNVs compared to age-matched mothers from the community sample. We also found that the frequency of anxiety symptoms was higher in mothers of children with CNV after the birth of their child with a CNV, compared to mothers from the community sample. Our findings highlight the need for the monitoring as

well as, where indicated, effective management of the mental health problems, not only of the children with pathogenic CNVs, but also their parents.

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Tables

Table 1. Socio-demographic characteristics of mothers of children with CNVs

Family ethnic background	
European	81%
Mixed	8%
Unknown	11%
Highest maternal educational qualification	
Low	7%
Middle	43%
High	31%
Unknown	19%
Family income	
<£9,999	6%
£10,000-£19,999	18%
£20,000-£39,000	31%
£40,000-£59,000	14%
£60,000+	17%
Unknown	14%

Table 2. Frequency of psychiatric problems in mothers of children with a CNV (N=272)

Psychiatric problems		After birth of child
	N(%)	N(%)
Depression	146(54%)	43(49%)
Sought treatment	121(84%)	
Received medication	108(74%)	
Hospitalized	13(1%)	
Anxiety	85(31%)	27(55%)
Sought treatment	61(73%)	
Received medication	46(55%)	
Hospitalized	3(4%)	
Panics	77(29%)	19(49%)
Sought treatment	39(48%)	
Received medication	31(39%)	
Hospitalized	2(3%)	
Phobias	56(21%)	5(16%)
Sought treatment	21(34%)	
Received medication	12(19%)	
Hospitalized	0	
Anorexia/Bulimia	31(12%)	5 (28%)
Sought treatment	15(48%)	
Received medication	3(10%)	
Hospitalized	2(7%)	
Other problems	34(13%)	7(37%)
Sought treatment	20(53%)	
Received medication	7(18%)	
Hospitalized	2(5%)	
Drink/Drug problems	15(6%)	1(10%)
Sought treatment	3(20%)	
Received medication	1(7%)	
Hospitalized	2(13%)	

Notes: N varies between instances, as not all participants responded to all items. The percentage of the 'after the birth of child' variable reflects the percentage out of those with the disorder.

Table 3. Comparisons of psychiatric symptoms' frequencies between mothers of children with a CNV and mothers from the community sample, as well as before and after the birth of the child.

	Mothers of children with a CNV (N=268)	Mothers from the community sample (N=2680)		
	Nsample/Ntotal	Nsample/Ntotal	χ^2	p
Ever Depression	142/268 (53%)	319/2680(13%)	311.69	<0.001
Sought treatment	120/142(45%)		207.74	<0.001
Medication	105/142 (39%)		147.2	<0.001
	Mothers of children with CNV (N=246)	Mothers from the community sample (N=2460)		
Anorexia	21/245 (9%)	59/2460 (2%)	29.4	<0.001
Bulimia	17/245 (7%)	61/2460 (3%)	15.7	<0.001
	Mothers of children with CNV (N=242)	Mothers from the community sample (N=2420)		
Alcohol abuse	10/242 (4%)	21/2420 (1%)	20.4	<0.001
	Mothers of children with CNV (N=244)	Mothers from the community sample (N=2440)		
Drug addiction	7/244 (3%)	11/2440 (0%)	19.5	<0.001
After the birth of the child**				
	Mothers of children with CNV (N=88)	Mothers from the community sample (N=176)		
	N(Nsample/Ntotal)	N(Nsample/Ntotal)	χ^2	p
Depression	43/88(48%)	77/176(44%)	0.62	0.43
	Mothers of children with CNV (N=84)	Mothers from the community sample (N=840)		
Anxiety	27/57(55%)	184/656(30%)	4.5	0.03
Mothers of children with CNV				
	CNV carriers (n=9)	Non-carriers (n=80)	χ^2	p
Depression	3(33%)	39/80 (44%)	0.77	0.38
Anxiety	2(22%)	19/80(24%)	0.01	0.92
Notes: Individuals were matched for their age at the time their child was born. 5 Mothers of children with CNV included in previous tables, did not have data on age, therefore they were not included in this analysis. There was no question available in ALSPAC that we could directly map to the ECHO study related to 'ever had anxiety disorders', but there was a question 'have you had anxiety since the birth of your child' which is included in the 'after the birth of the child' analyses **In the 'After the				

birth of the child' table, we selected mothers who had a psychiatric diagnosis and also data on whether the diagnosis was before or after the birth of their child. Out of 268 mothers of children with CNV, 88 mothers had complete information on whether their psychiatric diagnosis was before or after the birth of their child. They were matched in a 1:2 ratio with mothers from the community sample, because the total of the mothers from the community sample with data on depression and whether it was before or after the birth of their child was N=863.

Author contributions

Conceptualization of the study: MN, MvdB, study design: MN, MvdB, JH, MJO, IMAGINE-ID, data acquisition and analyses: MN, AC, SC, HM, MS, IMAGINE-ID, Interpretation of the results, writing, editing and reviewing drafts: all authors.

IMAGINE-ID Consortium Membership

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⁴ Unique – The Rare Chromosome Disorder Support Group, London, UK.

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	Amy	Lafont	1
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	Hayley	Tilley	1
	Husne	Timur	1
	Catherine	Titterton	1
	Neil	Walker	1
	Sarah	Wallwork	1
	Francesca	Wicks	1
Dr	Zheng	Ye	1
	Marie	Erwood	1
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	Philippa	Birch	2
	Samantha	Bowen	2
	Karen	Bradley	2
	Aimee	Challenger	2
Dr	Samuel	Chawner	2
Dr	Andrew	Cuthbert	2
Professor	Jeremy	Hall	2
Professor	Peter	Holmans	2
	Sarah	Law	2
	Nicola	Lewis	2
	Sinead	Morrison	2
	Hayley	Moss	2
Professor Sir	Michael	Owen	2
	Sinead	Ray	2
	Matthew	Sopp	2
	Molly	Tong	2
Professor	Marianne	van den Bree	2
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	Sarah	Davies	3
	Spiros	Denaxas	3
	Hayley	Denyer	3
	Nasrtullah	Fatih	3
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	Ellie	Kerry	3
	Anna	Lucock	3
Dr	William	Mandy	3
	Frida	Printzlau	3
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Dr	Susan	Walker	3
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IMAGINE-ID Clinical Collaborators

Title (if applicable)	First Name	Surname	Shorthand Institution	Genetics service	Hospital Trust
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