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ORIGINAL ARTICLE

Variants of unknown significance on chromosomal microarray analysis: parental perspectives

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Abstract Chromosomal microarray is the recommended first-tier genetic test when a child presents with idiopathic developmental delay (DD), intellectual disability (ID), and/or autism spectrum disorder (ASD). Microarray may discover variants of unknown clinical significance (VUS) and been suggested to cause parental stress and anxiety. A retrospective, mixed methods study investigated parental perceptions of chromosomal microarray results that contain VUS. Surveys were sent to parents of children with DD/ID/ASD following a VUS result to seek information regarding parental understanding of the result, perceived value, and perceptions of child vulnerability and parental stress. Parents reported that chromosomal microarray was important for understanding their child's diagnosis and they were satisfied with the information. A majority of parents reported high confidence in their ability to explain a VUS result to others. Of the parents who reported they received support, many reported that the support was from a genetic counselor. Based on these results, VUS results are important to parents of children with DD/ID/ASD and genetic counseling regarding VUS results contributes positively to both parental understanding and support.

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Introduction

When compared to G-banded karyotype and other cytogenomic analyses, chromosomal microarray (CMA) provides increased sensitivity for detection of chromosomal imbalances. This method of copy number variation (CNV) detection is currently recommended as a first-tier test by the American College of Medical Genetics for individuals with developmental delay (DD), intellectual disability (ID), and/or autism spectrum disorder (ASD), as well as multiple congenital anomalies that are not specific to a recognizable syndrome (Manning and Hudgins 2010; Miller et al. 2010). Even though this is a standard genetic test for individuals with DD/ID/ASD, there is much variability in laboratory interpretation and reporting of various CNVs (Bell et al. 2008; Kearney et al. 2011; Tsuchiya et al. 2009).

Understanding the underlying genetic etiology of DD/ID/ASD plays an important role in medical management (Coulter et al. 2011). When attempting to detect a genetic etiology for DD/ID/ASD, a variant of unknown significance (VUS) result is not uncommon. VUS results may lead to ambiguity due to the lack of uniformity in both CNV classification and information contained in the laboratory report. Determining clinical significance can be difficult due to the current lack of understanding or information about CNV pathogenicity (Tsuchiya et al. 2009). This ambiguity increases barriers to patient and family comprehension of the results (Reiff et al. 2012) For this reason, the medical community should assess how parents understand and assimilate a VUS result to identify resources that break down barriers and improve parental

comprehension of VUS findings (Reiff et al. 2012; Tsuchiya et al. 2009).

There have been few studies that investigated parental perceptions about VUS results after genetic testing on their child with ID. Makela et al. (2009) found that psychosocial validation (establishing proof for an existing, credible problem) was the most important outcome after a confirmed genetic diagnosis because it offered an etiological reason for the child's behavior(s) (Makela et al. 2009). Related studies have evaluated parental perceptions of a child's uncertain prognosis, life span expectations, and cognitive abilities after a confirmed genetic diagnosis of fragile X, Klinefelter, or Turner syndrome. Interestingly, Whitmarsh et al. (2007) revealed that families view genetic diagnoses in both a positive and/or negative light (often simultaneously), and parents were open to the uncertainties that come with these diagnoses (Whitmarsh et al. 2007). There have also been studies to further understand parental perceptions of "unknown" genetic results by assessing the impact of indeterminate newborn screening results and VUS genetics results in the cancer realm (Aatre and Day 2011; Ardern-Jones et al. 2010; O'Neill et al. 2009; Vos et al. 2008). These studies support an underlying theme: diagnostic uncertainty is an ongoing learning process. Presenting patients/families with uncertain test results gives rise to various opinions and attitudes regarding the recommended medical management for the child, the use of various genetic testing technologies, and the ways results are communicated to the parent/family. Despite these various studies, little research has been done regarding what a VUS result may provide the parent of a child with DD/ID/ASD. In this study, parents of children with a diagnosis of DD/ID/ASD and subsequent VUS results from CMA were surveyed to identify parental understanding of the result, perceived value, and perceptions of child vulnerability and parental stress.

Materials and methods

Participants

Eligible participants included parents/guardians of children with DD/ID/ASD who received a CMA result of unknown clinical significance through Lineagen, Inc. Participants were identified by licensed and certified genetic counselors through a comprehensive, de-identified chart review of patient medical records. All names and specific patient results remained unknown to the investigators. Due to the potential conflict of interest by two of the investigators, limited demographic information were collected in this study.

All patients were referred for CMA testing by their pediatrician or specialist. CMA results were provided to the ordering physician in the form of a physical binder and/or electronic pdf that included a description of the result at a middle school reading level. The information contained in the physical binder and/or electronic pdf (hereafter referred to as "report documentation") included background information regarding genetics, a description of the CNV, review of current literature, knowledge of associated features, and recommendations for appropriate follow-up. This report documentation was provided to the ordering physician approximately 1 month after test order. Each patient (and his or her parents) referred for testing in this study was provided the option to speak with a licensed/certified genetic counselor via telephone for pretest and posttest counseling sessions.

Procedures

This study was approved by the University of Utah Institutional Review Board. A total of 139 eligible participants were contacted via postal mail. Each participant was given a randomly assigned identification number to ensure confidentiality. These individuals were mailed the following documents: a recruitment/consent document, a paper survey, a "request to decline participation" postcard, an overview of the study (detailed information about the study's methods, participation process, and research objectives), study investigator and institutional review board contact information, and online survey hyperlink. Participants had the option of returning a copy of the physical paper survey or submitting online via Qualtrics® Online Survey Software. Reminders about this study were made on two occasions to those who had not replied. The first reminder was sent 30 days after initial contact via postal mail, and the second reminder 75 days after initial contact via email.

One of the surveys used in this study included 17 Likert scale and 6 open-ended questions. These 23 original questions were developed through iterative team-based meetings with investigators in the study (see Table 1). The survey was reviewed by graduate students in the field of genetic counseling for readability and clarity. The Parental Stress Index-Short Form and the Child Vulnerability Scale were also included for a total of 47 questions. The Parental Stress Index-Form has demonstrated good internal reliability (.87) (Abidin 1995), and the Child Vulnerability Scale has demonstrated acceptable reliability (.74) (Forsyth et al. 1996).

Quantitative data analysis

Responses to the 17 Likert scale questions were scored individually using a correlation matrix. This enabled identification of positive and negative correlations of statistical significance as well as determining general predictive themes. Correlations between variables of the originally created questions were assessed using Spearman's rho (to account for non-normal distributions of all data). Results were considered statistically significant at $p<0.05$. If data were analyzed as statistically

Table 1 Survey questions

1. Did you receive a binder of information regarding your child's result through Lineagen?
   (yes or no)
2. I feel that I can explain what an "unknown" finding is to other people
   (Strongly Agree, Agree, Disagree, Strongly Disagree)
3. How would/do you explain an "unknown" result in 3 sentences or less?
4. I feel I received ADEQUATE information from healthcare providers (i.e., medical geneticists, genetic counselors, physicians, nurse practitioners) regarding this genetic test result
   (Strongly Agree, Agree, Disagree, Strongly Disagree)
5. Because of the genetic information that has been provided to me, I feel…
   (Not at all overwhelmed, Somewhat overwhelmed, Very overwhelmed)
6. The things healthcare professionals tell me about my child's test result are…
   (Not at all confusing, Somewhat confusing, Very confusing)
7. Do you think this "unknown" result is the cause of your child's (ID/DD/ASD)?
   (Yes, No, I don't know)
8. I have further questions about what an "unknown" result means in general
   (Strongly Agree, Agree, Disagree, Strongly Disagree)
9. Overall, I feel that this genetic test was important for my child
   (Strongly Agree, Agree, Disagree, Strongly Disagree, I don't know)
10. Overall, how satisfied are you with the result and it's accompanied information pertaining to your child's genetic test result?
    (Very satisfied, Somewhat satisfied, Not at all satisfied)
11. The most important outcome of having this specific test result is…
12. The least important outcome of having this test result is…
13. Which of the following statements do you agree with most?
    This "unknown" result MAY be the cause of my child's ID/DD/ASD
    This "unknown" result IS the cause of my child's ID/DD/ASD
    This "unknown" result is NOT cause of my child's ID/DD/ASD
14. Do you feel you have received support regarding your child's "unknown" result?
    Yes (Please go to question 15a)
    No (Please go to question 15b)

15a. Who did you receive support from? (check all that apply)
   (Family/relatives, Friends, Genetic counselor, Doctor, Other healthcare professionals, My child's school system, Other family connections with similar results as that of my child, Other)

15b. What support system(s) would be most beneficial for you/your family? (check all that apply)
   (Family/relatives, Friends, Genetic counselor, Doctor, Other healthcare professionals, My child's school system, Other family connections with similar results as that of my child, Other)

16. Regarding my child's results, I have spoken to (check all that apply):
   (I have no spoken to anyone, Medical geneticist, Genetic counselor over the phone, Genetic counselor in person, The healthcare provider who ordered my child's CMA test, Other)
17. I understand that my child's genetic testing result…
   (Will never be reclassified, Will be reclassified as benign (not likely causative) or pathogenic (causative) as more information surfaces, May or may not be reclassified)
18. How did this "unknown" result change your understanding of your child's ID/DD/ASD?
19. Since receiving my child's result, his/her medical management has…
   (Completely changed because of the result, Slightly changed because of the result (in some aspects, but not in others), Not changed at all (the same as before receiving the results))
20. If your child's medical management has changed for any reason because of this result, please explain these changes.
21. I have told family/relatives about my child's genetic testing results for the following reasons:
    I have NOT told family/relatives—If not, why?
    Their support
    Their advice
    It is useful for my family to know about genetic information

Table 1 (continued)

To be more accepting and/or understanding of our child
They have (or may have) the ability to aid in my understanding of the information the healthcare professionals gave me
Other:
22. After receiving the genetic testing result, I believe my child's ID/DD/ASD is due to:
(Environmental contributions, Genetics, A combination of both the environment and genetics, Neither, I don't know)
23. If you were to have another child would you have him/her tested for this same "unknown" result/genetic change as a newborn?
Yes—Why?
No—Why?

significant, the strength of the correlation was then determined using a correlation matrix. All analyses were performed using Stata Statistical Software: Release 12®. College Station, TX: StataCorp LP (2011). Responses to the Parental Stress Index Subscale and the Child Vulnerability Scale were totaled and then analyzed in conjunction with the remaining survey questions to assess any subscale agreement(s) and shared themes. Subscale question agreement was assessed using Cronbach's alpha coefficient. Cronbach's alpha coefficient was used in order to correlate the entire validated instrument to individual survey questions, rather than identifying correlation strength between single questions as done previously using Spearman's rho. Additionally, each individual question's contribution to the overall fit was assessed.

Qualitative data analysis

The survey included six open-ended questions. Major thematic categories were distilled inductively from the written responses using a content analysis (Miles and Huberman 1994). A coding template was developed based on reading of all the responses to each of the questions and then systematically applied to all of the responses by one of the investigators. The codes served as labels to assign meaning to specific data and were used to retrieve, organize, and compare data within distinct categories. Categories and written summaries of the data were reviewed by the research team to ensure trustworthiness and rigor of the analysis (Miles and Huberman 1994).

Results

Of 139 contact participants, 30 submitted a completed survey, resulting in a 21.6 % response rate. The responses that reached statistical significance (p value=0.05) and had a strong correlation (either negative or positive) are included in Table 2. In addition to reaching statistical significance, these responses also have a Spearman's rho correlation value equal to or less than −0.418 (consistent with strong negative correlations) or equal to or greater than 0.420 (consistent with strong positive correlations). Negative and positive correlations quantify the degree to which two measureable variables, X and Y, "go together." A negative correlation will exist when high values of X are associated with low values of Y. Conversely, a positive correlation will exist when high values of X are associated with high values of Y. With regard to this study, "X" and "Y" refer to the survey questions that were responded to in such a way that correlations were identified.

The significant results from the data analysis in Table 2 indicate those who received adequate information about the VUS reported the results were not confusing and these participants were not overwhelmed. In addition, those who received report documentation also responded correctly on what was the definition of a VUS and that they received appropriate amount of support. However, participants who reported they received adequate information were also significantly correlated with questions remaining. Interestingly, those who responded the VUS result were confused and had few to no questions about the meaning of it. Finally, participants who reported that they do not believe VUS is not the cause of their child's diagnosis do not know what is the cause.

Eighty percent (24 of 30) of respondents reported that the CMA result and the report documentation were important to them. Sixty-six percent (20 of 30) of respondents reported that they received adequate support regarding their child's unknown result (Q14). The remaining 33 % (10 of 30) reported that they did not receive the desired support to best cope with a VUS result. Of the 20 participants who received adequate support, 14 indicated that support was received from a genetic counselor. The Child Vulnerability Scale and Parental Stress Index Subscale were analyzed with the originally created survey questions using Spearman's rho correlation arrays. There were no statistically significant results with these validated instruments.

We also explored the parents' perceived value of the VUS result. To assess this aim, we asked participants to provide information regarding whether they found this test to be important to them even though information on their child's CNV is limited. Table 3 summarizes the qualitative responses. Eighty percent (24 of 30) of respondents stated that receipt of the result was important. We asked parents to then clarify what they thought was the most important outcome(s) of the test result that was obtained. Responses were categorized into four categories: 1) confirmation of potential genetic cause; 2)

Table 2 Statistical significant correlations with strong associations

Positive correlations	Questions from Table 1	*p* value
Those who reported receiving adequate information regarding VUS result did not report results as confusing.	Q4 and Q6	0.0002*
Those who reported little confusion, also report being the least overwhelmed by test result.	Q5 and Q6	0.021*
Those who reported receiving report documentation also understand the VUS may, or may not, be the cause of their child's ID/ASD/DD.	Q1 and Q13	0.0003*
Those who reported to have received adequate information also reported receiving appropriate support.	Q4 and Q14	0.0055*
Those who reported to believe the VUS is *not* the cause of their child's ID/ASD/DD report they do not know what the cause is, though it is believed not to be the VUS.	Q22 and Q7	0.0054*
Reported receiving adequate information, though still having questions about the result.	Q4 and Q8	0.0049**
Reported the result as confusing, though having few to no questions regarding the results' meaning.	Q6 and Q8	0.0215**

*Positive correlation

**Negative correlation

important information for medical management; 3) the parental relief and; 4) diagnostic rule out of other serious conditions. Some specific participant responses are as follows:

> Having somewhat more information and more of an "answer" or explanation.
> For the diagnosis later if a stronger link is established through future research. It has also helped in getting therapies, insurance coverage, etc.
> Knowing that there still could be a genetic reason for my son's DD/ID/ASD.

We asked participants to write their interpretation of a VUS in their own words. Responses from participants who did receive report documentation:

> It is a lack of understanding of the genes/mutations of genes/deletions of genes in a chromosome and how those may or may not affect the person with those affected areas. There is not enough research to understand the effects of those issues.
> She has a duplicate band on chromo #16, which may indicate autism, learning disabilities, etc. Enough

Table 3 All qualitative responses and recurring themes are presented here (thematic categories of responses that had less than 4 were not included)

Question	Number of responses	Thematic category description
Question 4—How would/do you explain an "unknown" result in three sentences or less?	14	A mutation without enough information to conclude definitively
	6	Mutations that don't indicate a known/already identified syndrome
	5	A deletion/duplication
Question 11—The most important outcome of having this specific result is…	8	Giving us more information about my child's health in general
	7	That it may be causal
	5	To rule out other diagnoses
Question 12—The least important outcome of this test result is…	10	Not having a definitive diagnosis
	4	Having an uncertainty about my child's future
Question 18—How did this unknown result change your understanding of your child's ID/ASD/DD?	13	Did not change understanding of ID/ASD/DD
	9	May be causal/insight to genetic contributions
Question 20—If your child's medical management has changed for any reason because of this result, please explain these changes…	6	Further medical consults for symptoms
Question 23—If you were to have another child, would you have him/her tested for the same "unknown" result/genetic change as a newborn?	7 responded Yes	For anticipatory guidance with medical care
	12 responded No	Reasons provided: My other child/children is/are without symptoms, cost, no diagnosis was gained, and the cause is environmental

> research hasn't been done to be totally conclusive, but there is a suspected link.
> The results were indeterminate. There is part of a chromosome missing but experts/doctors do not know what that means. Testing and research continues

Responses from participants who did not receive report documentation:

> More or less of a chromosome with no link to any known developmental delay, autism, Asperger's. Not enough research of people with the same thing. It's rare.
> Findings of a reading that matches the child and one of the parents DNA.
> The [gene] is a possibility based on (NHGRI 2004) studies. Scleroderma is presented in her makeup. I don't know what there is to do now, if anything?

Participants were also asked how the VUS may change their understanding of their child's condition. Interestingly, almost all of the responses indicated that it did not change their understanding and/or it reinforced their opinion that the child's condition was genetic ("It did not change my understanding."; "It has not changed the understanding of my child's ASD."; and "Gave some explanation but not a ton of understanding."

A question was asked about how the child's medical management might change as a reason of the VUS, and most of the responses reported that it would help them be aware of symptom presentation and further medical consults for the symptoms. Representative quotes include:

> It caused me to be diligent in watching for any signs of seizures-children with autism typically have a great risk for seizures than others.
> Physical therapy was added and daily medications
> We added occupational water therapy to the OT and speech. I also plan to join a monthly support group.

Finally, participants were asked if they would have another child undergo genetic testing, and most responses were no. Reasons included cost, not unless the other child had symptoms, there would still not be a diagnosis, and the participants were already aware of symptoms and interventions.

Discussion

This study investigated parental understanding of a VUS result after their child had undergone CMA testing for clinical features including DD/ID/ASD. Three aspects were assessed: parental understanding of the result, perceived value, and perceptions of child vulnerability and parental stress. In our assessment of parental understanding of a VUS result, genetic counseling regarding specific VUS results along with written materials contributed to parental comprehension of the unknown result. These results are similar to other research studies in that parental comprehension increased with additional counseling and when supplemental information was provided (Reiff et al. 2012). In our study, of the 26 participants who received report documentation, 25 of those understood that a VUS result may be the cause of their child's DD/ID/ASD although current literature does not allow for a definitive assessment of pathogenicity for the test indication(s). This was further supported with responses to open-ended questions about the most important outcome (Q11) and medical management (Q20) indicating that the VUS provided some causal explanation for their child's condition and guidance for future medical care. However, many of the responses to the open-ended questions (Q18 & Q23) indicated that the test result did not change their understanding of ID/ASD/DD and that most participants would not undergo genetic testing with another child. Of note, those respondents who received report documentation had a number of remaining questions, which could indicate they are more invested in their understanding of the VUS and eventually learning what it means for their child. Similar to other research studies, this study demonstrates that while families comprehend a VUS result, they still struggle to "make meaning" of the result and potential implications for their child.

These results raise questions about the ethical implications of VUS and how to best disclose them to families without causing additional stress or anxiety. Although there were no statistically significant correlations found with perceived child vulnerability and parental stress surveys, these results may be due to the timing when the parent received the VUS. As stated in the qualitative responses, many of the participants stated the VUS provided some explanation and "parental relief" for their child's diagnosis, which in itself can reduce parental stress and child vulnerability. Participants also wrote that the VUS helped with medical management and ruling out other conditions which may reduce parental anxiety and stress. Future research may want to assess how parental stress and anxiety change before and after a VUS result and compare with parents who did not get any positive results for their child with DD/ID/ASD. It may be the lack of any positive genetic result to explain a health issue in a child may cause more parental stress and anxiety.

These results highlight that there is a need for different and/or additional education and support as families struggle with complex genetic information such as VUS (Reiff et al. 2012). More research assessing the impact of VUS on families is important to understand how to support and inform families that pursue genetic testing for rare disorders. Specifically, longitudinal research on how families cope and manage their child's diagnosis to identify mechanisms for support would be useful.

Though statistical significance and qualitative data saturation were obtained, there was a small sample size and response rate within this population. Some methodological limitations should be taken into consideration. All participants received their CMA testing through Lineagen and voluntarily participated in this study. These experiences may differ from other patient populations, including those who declined participation. Participant demographic data were not collected, which limits generalizability. The time span from participants receiving their CMA results to survey completion varied: some completed the survey 1 month after the VUS result while others completed the survey 1 year after the VUS result. This limitation could have resulted in recall/information biases. Finally, response rate was low and additional efforts to recruit parents with a child with DD/ID/ASD may be required.

In summary, this study assessed parental perceptions of a VUS discovered after CMA testing in children with clinical features including DD/ID/ASD. This study supports the notion that parents value a VUS result, and a positive genetic test result, even though it may be a VUS, was important for medical management and to rule out other conditions. In addition, those who received report documentation about their child's result seemed to have a better understanding of a VUS when asked to provide their own explanation of the result, and those who spoke with a genetic counselor had increased knowledge about VUS results in general. However, participants still struggled with meaning and future implications of the VUS. Larger studies that assess parental stress, anxiety, and knowledge before and after genetic testing and include participants with varied health literacy levels are needed. Furthermore, research needs to explore the type of test result including negative, positive, or VUS to better understand what specific information and techniques are most beneficial throughout the testing/communication process.

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Compliance with ethics guidelines All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Conflict of interest The authors have no conflict of interest to disclose.

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