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Changes in Gene Sequence that Cause Discordances Involving Disease in Monozygotic Twins

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Abstract

Identical twins or, monozygotic twins, occur when the egg in a mother is fertilized, but one zygote divides into two separate embryos. Monozygotic twins are considered to be genetically identical, but most twins often display discordances, some involving diseases or disorders. Some of these differences are due to environmental factors. For example, one twin may have diabetes due to diet. Recent literature has shown that some differences in monozygotic twins may be due to changes in gene sequence, as opposed to random, environmental or epigenetic factors. Identical twins from pedigrees with familial disease often show discordances. When looking at schizophrenia specifically, the discordance rate is about 50%. This poster is a literature review about specific de novo variants, duplication, overlaps, and even a rare deletion in an affected twin, which provides evidence a specific mutation contributes to a particular disorder. These findings in monozygotic twins will further research that provides information on how to treat or prevent disorders that are caused by genetic changes.

Figure from M. Laplana, JL. Royo, et al.

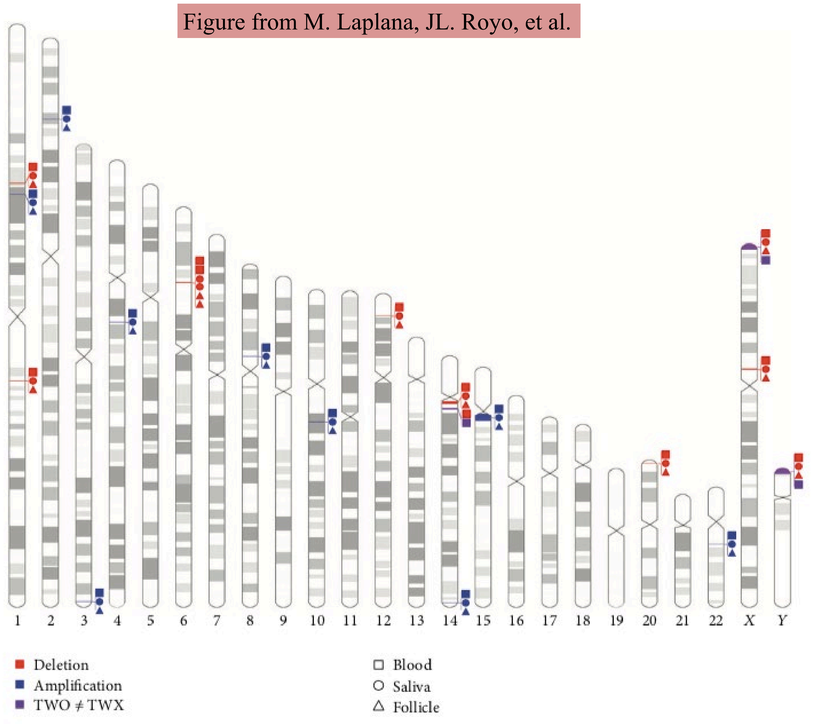

Figure 1: Summary of copy number variant (CNV) regions in both twins of one family, purple indicates regions that differ between twin 1 and twin 2

- In this study, array comparative genome hybridization (CGH) was used to compare genomes in the affected and unaffected twin to identify CNVs involving deletions and amplifications. Red and blue identify the specific regions where the specific CNVs occurred.
- The purple identifies the areas where regions of the chromosomes in twin 1 and twin 2 are not equal. This shows that changes in gene sequences play a role in a twin being affected by autism spectrum disorder (ASD).
- In the affected twin, there were 59 total genes that changed in the twin with ASD, four of them (*HUWE1, TUBGCP5, ASMT,* and *PCDH15)* were found in an autism database and have previously been associated with the disease.
- The most consistent CNV region with potential association to ASD was chr15:20172544-22835945.
- Amplifications in 15q11-q13 regions have been associated with developmental disorders including ASD.

Figure adapted from M. Laplana, JL. Royo, et al.

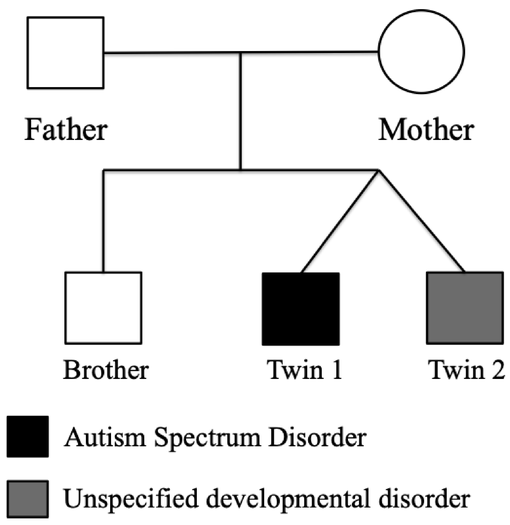

Figure 2: Family pedigree of ASD cases reported in a family with asymptomatic parents and at least one affected twin.

- In the study following, complete genome sequencing was used in each twin to identify CNVs, along with other factors like structural variation (SV), single nucleotide variants (SNV), and substitutions. The researchers then made a list of the top 20 canonical pathways to differentiate between the shared and unshared pathways found only in the affected twins to compare and contrast.
- The researchers also used ingenuity pathway analysis (IPA) to identify what pathways in each twin were affected. Pathways that were altered in both affected twins may correlate with some of the disease symptoms. Examples of altered pathways that occurred in both affected twins include; glutamate receptor signaling, synaptic long term potentiation, synaptic long term depression, and dopamine feedback in cAMP signaling. The top 5 pathways identified in each affected twin have to do with neural functions.
- A high percentage of CNVs (4 out 5 in the affected twin in family 2) were not identified in either parent, suggesting that this disease is multifactorial with some causes due to de novo changes in gene sequence.

Figure adapted from C. A. Castellani, M. G. Melka, et al.

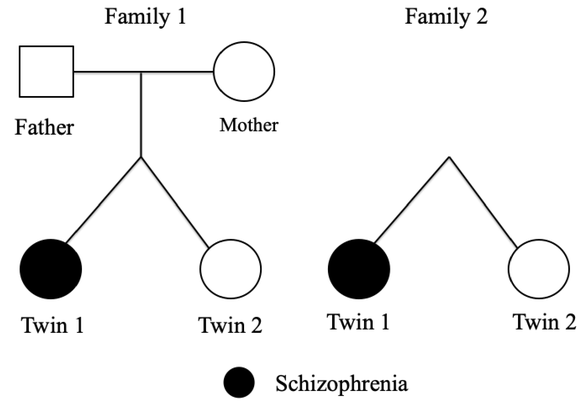

Figure 3: Family pedigree of schizophrenia cases in two different families, with parents in at least one family being asymptomatic

Tables adapted from C. A. Castellani, M. G. Melka, et al.

Chromosome	Cytoband	Size (bp)	CNV Type
5	5q23.1	2000	Deletion
9	9p24.1	10,000	Deletion
10	10p12.1	4000	Deletion
14	14q11.2	14,000	Amplification
15	15q11.2	70,000	Amplification
16	16p11.2	48,000	Amplification
16	16q12.2	14,000	Amplification

Copy number variants unique to the affected twin in family 1

Chromosome	Cytoband	Size (bp)	CNV Type
5	5p15.1	8000	Deletion
5	5p11	2000	Amplification
5	5q31.1	6000	Deletion
12	12q24.21	8000	Amplification
14	14q32.33	4000	Amplification

Copy number variants unique to the affected twin in family 2

Figure 4: Copy number variants unique to the affected twins with schizophrenia in families 1 and 2. This data shows that this disease affects similar chromosomes in the affected twins of different families.

In studies, there have been similarities of CNVs in discordant twins from different families with the same disease. Using gene sequencing in discordant monozygotic twins with the same disease can give geneticists crucial information on the specific regions on chromosomes that are affected by certain diseases. Certain pathways can also be identified, which can give great insight in research on the symptoms of these diseases and potentially how to treat or cure them.

References

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Acknowledgements

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