Evidence of transgenerational effects on autism spectrum disorder using multigenerational space-time cluster detection

Rebecca Richards Steed, Amanda V. Bakian, Ken Robert Smith, Neng Wan, Simon Brewer, Richard Medina, and James VanDerslice

Abstract

Background: Transgenerational epigenetic risks associated with complex health outcomes, such as autism spectrum disorder (ASD), have attracted increasing attention. Transgenerational environmental risk exposures with potential for epigenetic effects can be effectively identified using space-time clustering. Specifically applied to ancestors of individuals with disease outcomes, space-time clustering characterized for vulnerable developmental stages of growth can provide a measure of relative risk for disease outcomes in descendants.

Objectives: (1) Identify space-time clusters of ancestors with a descendent with a clinical ASD diagnosis and matched controls. (2) Identify developmental windows of ancestors with the highest relative risk for ASD in descendants. (3) Identify how the relative risk may vary through the maternal or paternal line.

Methods: Family pedigrees linked to residential locations of ASD cases in Utah have been used to identify space-time clusters of ancestors. Control family pedigrees of none-cases based on age and sex have been matched to cases 2:1. The data have been categorized by maternal or paternal lineage at birth, childhood, and adolescence. A total of 3957 children, both parents, and maternal and paternal grandparents were identified. Bernoulli space-time binomial relative risk (RR) scan statistic was used to identify clusters. Monte Carlo simulation was used for statistical significance testing.

Results: Twenty statistically significant clusters were identified. Thirteen increased RR (> 1.0) space-time clusters were identified from the maternal and paternal lines at a p-value < 0.05. The paternal grandparents carry the greatest RR (2.86–2.96) during birth and childhood in the 1950's–1960, which represent the smallest size clusters, and occur in urban areas. Additionally, seven statistically significant clusters with RR < 1 were relatively large in area, covering more rural areas of the state.

Conclusion: This study has identified statistically significant space-time clusters during critical developmental windows that are associated with ASD risk in descendants. The geographic space and time clusters family pedigrees with over 3 + generations, which we refer to as a person's geographic legacy, is a powerful tool for studying transgenerational effects that may be epigenetic in nature. Our novel use of space-time clustering can be applied to any disease where family pedigree data is available.

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Keywords: Transgenerational, Space-time clusters, Autism spectrum disorder

Introduction

Autism spectrum disorder (ASD) is a complex developmental syndrome that affects one in 44 children born in the United States as of 2021 according to the Centers for Disease Control and Prevention (CDC) [1], and Utah’s most recent published rate, one in 44 children in 2018 (https://www.cdc.gov/ncbddd/autism/addm-community-report/executive-summary.html) [2]. The disorder is characterized by neurodevelopmental characteristics and behaviors that vary in severity, impacting learning, communication, and social interactions [3–5]. The etiology of ASD is complex and includes both environmental and genetic factors [6–8]. As biotechnology has improved, the capacity for studying genetics and heritability has improved with the ability of genetic testing for ASD as more investigators have shown that ASD is highly heritable (heritability rates 0.61–0.73) [5, 9–12]. Through these efforts associations from maternal and paternal genetic variants show an increased risk for ASD [13, 14]. The genetic risks do not diminish findings that environmental factors that play a role in disease outcomes. Ambient air pollution exposure from polyaromatic hydrocarbons of roadway air pollutants, nitrogen dioxide, and particulate matter during vulnerable developmental windows of growth has been associated with increased risk of ASD and its severity [15–20]. Endocrine-disrupting chemicals, gestational infections, early life infections, and stress have also been found to contribute to the risk of ASD [21].

One intersection between the two etiologies of environment and genes can be epigenetics. Epigenes are small marks or switches on DNA that can silence or activate portions of DNA, essentially changing gene expression [22, 23]. Epigenetic mechanisms have been proposed as potential means by which environmental exposures in previous generations (2 + generations) might exert increased risks in future generations and induce increased levels of heritability [24, 25]. DNA methylation, histone modification, and RNA silencing are epigenetic mechanisms by which the environment acts on gene expression [26, 27]. Rett syndrome and Fragile X syndrome (FXS) are common comorbidities with ASD and show firsthand evidence of epigenetic methylation and non-binding RNA effects as mechanisms for ASD outcomes [28]. Exposures to nickel, cadmium, mercury, arsenic, pesticides, and other gases and particulates [29], all of which are considered environmental pollutants, have been found to impact epigenetics that contribute to disease outcomes across generations [28]. Epigenetic changes may originate during the ancestor’s (parents, grandparents, or previous ancestor) vulnerable developmental stages of growth, such as the prenatal and birth stage when developmental programming of organs is underway, and exposures occur [30]. Direct-contact exposure studies for the exposed generation have shown neurological impairment from certain exposures [31]. Perera et al. found that higher concentration exposures to incomplete fossil fuel combustion between gestation and 5 years of age resulted in statistically significantly lower IQ, and verbal scores [31]. Animal studies have confirmed transgenerational effects from environmental exposures [25]. Controlled laboratory settings simulating environmental pollution exposures from pesticides, fungicides, heavy metals, and petrochemicals have shown transgenerational effects in mice models [25, 32]. For the study of human subjects, challenges remain in testing the hypothesis that environmental exposures of ancestors’ affect ASD outcomes in progeny.

Space-time cluster analysis is one method used for exploratory research of environmental effects for hypothesis development. Among other things, it is used to align complex data and examine patterns of individuals with a disease suspected to be associated with an environmental exposure spatially and temporally [33, 34]. It can be extended as an approach for examining potential transgenerational effects of an environmental risk factor by identifying spatial-temporal patterns of grandparents and parents of individuals that have a health outcome associated with an environmental factor. The approach can be used to identify whether ancestors of ASD cases shared the same space and time, implying that there could be common factors (i.e., environment) elevating the risk of ASD among their descendants [35, 36]. Some diseases have been shown to originate during periods when growth and development are most susceptible to environmental stimuli (e.g., gestation when programming of specific organs is underway, or during childhood, adolescence, or preconception when rapid growth and development occur) [26, 30, 31, 37]. The approach can be further refined by focusing on these same developmental ages during ancestors’ lives in space-time cluster analyses. Using geographic residential data to investigate and identify the shared environmental space and time of parents and grandparents related to a child diagnosed with ASD could shed light on increased risks, vulnerable
developmental windows that may be more susceptible to exposures and disease outcomes and provide evidence regarding whether there is a greater risk for disease of descendants associated with ancestral environmental exposures.

The aims of this study are to (1) Identify space–time clusters of parents and grandparents of children with a clinical ASD diagnosis and their matched controls. (2) Identify developmental windows of parents and grandparents with the highest relative risk for ASD in their children/grandchildren. (3) Identify how the relative risk may vary through the maternal or paternal line.

Methods
Study design
A retrospective space–time cluster analysis was used for the study design. Residential locations of parents and grandparents of clinically diagnosed ASD cases in Utah from 1989 to 2014 were compared to the residential locations of the ancestors of matched controls. This design is like other space–time cluster analyses of health outcomes, with the outcome defined as having a child/grandchild who has been clinically diagnosed with ASD. However, our design uses the ancestor generation(s) as the point of interest. The cluster analysis was carried out in six separate models for six types of ancestors: mothers, fathers, maternal grandmothers and grandfathers, and paternal grandmothers and grandfathers. For each of these groups, separate cluster analyses were applied for three periods of their lives, referred to as ‘vulnerable developmental windows’, representing windows of increased vulnerability to adverse effects of environmental stressors: birth/infancy (age 0–1 year), referred to as the “birth” window from this point on in the paper, childhood (age 2–11 years), and adolescence (age 12–17 years) [37] making it a total of 18 models for analysis.

Inclusion criteria
For transgenerational research, the important exposure group is the ancestors of individuals with an ASD diagnosis. The individuals with ASD were not used in the modeling and analysis. They were used only to find their ancestors to build their family pedigrees. Ancestors of the ASD cases were defined as the eligible parents/grandparents of individuals with a clinical diagnosis of ASD with a birth year between 1989 and 2014. The Utah Registry of Autism and Developmental Disabilities (URADD) was the source of the ASD individuals. URADD classifies ASD individuals using a spectrum of diagnostic billing codes (ICD 9 29,900, 29,901, 29,910, 29,911, 29,980, 29,981, 29,990, 29,991 and ICD 10 F84.0, F84.2, F84.3, F84.5, F84.8, F84.9). The parent/grandparent cases used in the analysis were linked to the URADD individuals using the Utah Population Database (UPDB), an extensive multi-database repository that can generate family pedigrees from administrative data. Non-case ancestors were identified in the UPDB and defined as parents/grandparents of the randomly selected children matched on age and sex of case children born between 1989 and 2014. These parents/grandparents were included in the study if they met the following criteria: (1) the diagnosed child was the first reported case of ASD in the family according to the records in URADD linked to the pedigree data in UPDB; and (2) the parent/grandparent had a Utah birth certificate, a Utah medical record during childhood (age 1–17), and/or a record of a Utah driver’s license. The ASD child birth years in the data range from 1989 to 2014, parent birth years range from 1949 to 1995, and grandparent birth years range from 1929 to 1977 (Fig. 1). Family Pedigree and Data Structure is a graphic that gives a visual overview of our family case and none-case selection structure.

Residential history
Residential locations for the parents and grandparents of the ASD case and control children were obtained from the UPDB. Residential locations came from several administrative sources from the UPDB. Specifically, birth certificates were used to locate parent’s and grandparent’s residences at their time of birth. Medical records, including inpatient records, All Payers Claims, and Emergency Department records were used to place the parents and grandparents in childhood at residential locations. Medical records and driver’s license records were used to identify the residential location of parents and grandparents during adolescence.

Cluster analysis
A spatial scan statistic Bernoulli space-time binomial distribution model was used to identify space-time clusters for each group of ancestors at each of the three exposure windows. The Bernoulli model is a discrete binomial distribution scan statistic that tests for binary outcomes; ‘case’ or ‘non-case’ present in a population at any given place and time using varying size elliptical cylinder windows [38–40]. One of the advantages of using the Bernoulli distribution is its sensitivity to point-level location data in case and non-case populations. The statistical significance of each cluster (p < 0.05) was estimated using Monte Carlo simulation with 999 permutations representing the random placement of cases. A Bonferroni-corrected p-value was calculated to control for Type I error [41]. A scan statistic then computed and compared the maximum likelihood ratio from the dataset to randomly generated permutation datasets with the
assumption there are no clusters. The maximum likelihood ratio test was used to identify the most likely cluster to have occurred in the analysis. A relative risk value for each cluster was then calculated by using the estimated risk within each space-time cluster divided by the estimated risk outside of the cluster [38].

Many case and non-case ancestors did not change residential locations over time, particularly between birth and childhood time periods. As such, a cluster arising from a factor present during the birth window may also be detected for the childhood exposure window of the parent or grandparent. To assess whether identified clusters within the same ancestor group were distinct or comprised of the same individuals, we determined the number of subjects in a cluster who also fall within the space of another cluster, as shown in the Additional file: 1 Table S1. Overlap Analysis Results.

Residential locations were tested for spatial autocorrelation to identify areas that might get over-predicted in the binomial distribution cluster analyses. An over-prediction can occur if location points are dense in any given area [42]. As expected, spatial autocorrelation is present for one area with the highest population density in the state. However, no spatial clusters were identified for our cluster areas.

Results
The study used 3957 individual ASD cases to link 7914 parents and 15,828 grandparents over space and time, matched 2:1 at the case level for age and sex (Table 1). Number of Subjects and Ranges of Birth Years by Relation provides breakdown of our general data and what we had available to use.

Our analysis found 64 space-time clusters among case families, 20 of which are statistically significant (<0.05). The 20 clusters occurred between 1930 and 2002, seven with RR < 1.0 (See Figs. 2, 3, 4, 5, Table 2). Seventeen had p-values < 0.01, and three had p-values 0.01 < p < 0.05. All ancestor types of ‘parent’ or ‘grandparent’ have birth and childhood clusters. Only one cluster was associated with the Adolescent window (Maternal Grandmother, \( RR=0.06 \)) of 13 clusters with \( RR>1 \) (range = 1.27–2.96). Nine of the 13 clusters are among grandparents four are among parents. Eleven of the thirteen clusters range in the narrow time window of 1946–1960. Parent clusters are larger in area size (1633–4248 km²) than the grandparent birth and childhood residential location clusters and have \( RR>1.2 \). Three clusters among maternal grandparents with RR between 1.0 and 2.0 occurred in predominantly urban areas.

A cohort effect was observed between two cluster pairs. Spatially overlapping clusters of birth #1 cluster
### Table 1  Number of subjects and Ranges of Birth Years by Relation

| Family relation (birth year range) | Percent linked to a residential location (%) | Total subjects | Infant | Childhood | Adolescence |
|-----------------------------------|---------------------------------------------|----------------|--------|-----------|-------------|
|                                   |                                             |                |        |           |             |
| Mother (1948–1998)                | 91                                          | Case, n = 3957 | 3957   | 2734      | 2993        |
|                                   |                                             | Non case, n = 7914 | 7914   | 5468      | 5986        |
| Father (1925–1997)                | 93.5                                        | Case, n = 3957 | 3957   | 3994      | 2374        |
|                                   |                                             | Non-case, n = 7914 | 7914   | 7914      | 4748        |
| Maternal grandmother (1903–1982) | 92.5                                        | Case, n = 3924 | 1705   | 2861      | 783         |
|                                   |                                             | Non-case, n = 7848 | 3410   | 5722      | 1566        |
| Maternal grandfather (1973–1975)  | 92.5                                        | Case, n = 3774 | 3584   | 3289      | 929         |
|                                   |                                             | Non-case, n = 7548 | 7168   | 6578      | 1858        |
| Paternal grandmother (1907–1977) | 90.5                                        | Case, n = 3924 | 1644   | 2855      | 1119        |
|                                   |                                             | Non-case, n = 7848 | 3288   | 5710      | 2238        |
| Paternal grandfather (1897–1977)  | 91.3                                        | Case, n = 3795 | 1644   | 3336      | 1063        |
|                                   |                                             | Non-case, n = 7590 | 3288   | 6672      | 2126        |

**Fig. 2  Clusters of Residential Locations of Mothers of ASD Cases in Utah**

- **Cluster # 3 Maternal (Birth)**
  - RR = 0.37, p = 0.034
  - 1972 - 1983
  - N Observed = 18
  - N Expected = 48

- **Cluster # 4 Maternal (Childhood)**
  - RR = 1.20, p = 0.0 - E13
  - 1955 - 2000
  - N Observed = 1,272
  - N Expected = 1,059

- **Cluster # 1 Maternal (Birth)**
  - RR = 1.31, p = 0.0 - E12
  - 1966 - 1995
  - N Observed = 1,557
  - N Expected = 1,326

- **Cluster # 2 Maternal (Birth)**
  - RR = 0.72, p = 0.0 - E8
  - 1959 - 1984
  - N Observed = 409
  - N Expected = 560

**Mother Cluster Key**
- Mother's RR < 1
- Mother's RR > 1

**Legend**
- Light Green: Mother's RR < 1
- Purple: Mother's RR > 1

- N: North
- E: East
- 50 Miles
share 42.6% membership with childhood #4 cluster from the maternal lineage. Paternal birth cluster #11 shares 48% membership with childhood cluster #13. The overlapping membership signifies individuals that did not move between vulnerable developmental windows and contributed to statistically significant space–time clustering for the next vulnerable developmental window from the same lineage group. Though most of the clusters overlap in space and/or time, very small, or no shared membership was found between developmental window clusters and lineage between other statistically significant clusters (see Table 2).

Of the seven clusters with lower risk (RR < 1), five are from the maternal side of the family, with four divided between the mother and father. All are in rural areas, with six of the seven occurring in the northern part of the state (Figs. 2, 3, 4). Compared to these clusters, clusters with RR > 1–1.49 are larger (area = 98–3247 km²), longer in duration (18 to 52 years), are predominantly urban, and are both maternal and paternal.

Approximately 9% of the address records were associated with PO Boxes in rural areas. We used a sensitivity analysis to assess potential bias in these locations. We moved cluster points 10 m in random directions and re-ran the space–time cluster analysis. The clusters remained, although rural clusters lost their statistical significance.

Discussion

To our knowledge, this is the first transgenerational space–time cluster analysis to study ASD health outcomes in progeny. Our study has used space–time cluster analysis as a novel means of exploring transgenerational risk using residential locations and time windows of parents and grandparents of ASD case children during vulnerable developmental windows of exposure. We identified
20 statistically significant space-time clusters of residential locations of parents and grandparents of varying size, duration, and varying levels of risk. The identified clusters are diverse in location, with a general trend toward spatially smaller sized clusters located in more urban areas for their time durations, and larger sized clusters with a mixed composition of largely rural areas with some urban areas based on Census designations from 1960 to 2000 for applicable clusters [43]. Census records with designations predating 1960 for Utah are not available. Therefore, decisions about rurality and urbanicity were made based on 1960 classifications, with the presumption that rural areas would still be rural in 1960, and urban areas predating 1960 would still be urban in 1960 [43].

It has been posited that the urban–rural trend in our results is a consequence of reporting bias, where cases are less likely to be reported in rural locations [44]. However, for our analysis it is the ancestors used in statistical calculations, not the ASD case children themselves. Additionally, the urban–rural trend we observed in our results has also been observed in Swedish ASD studies [45].

Transgenerational research requires extended family pedigree analysis with the ability to identify exposures of ancestral generations that are no longer present in affected generations [25]. This study was able to take the initial steps in accomplishing this in a novel way with the use of space-time cluster analysis of ASD using grandparent and parents of ASD case’s residential histories in early life. Space-time clusters provide the location and time of a shared space, which can be used to generate hypotheses regarding the underlying factors associated with those places and times that might be the explanatory, putative, and underlying factors that produced the health outcome in progeny. The putative factors could be any condition or conditions present at those locations and time periods where
individuals were more likely to share conditions including environmental contaminants, including endocrine-disrupting chemicals, dietary patterns, and nutritional deficiencies, or heightened psychological stress resulting from social or economic conditions [46]. Effects may be dependent on maternal or paternal inheritance and transmission. Paternal grandparent nutrition in childhood, for instance, directly impacts sex-specific health outcomes in grandchildren [47]. Clusters from our analysis with the highest RR s are from the paternal grandmother and grandfathers, occurring at a time when it was common to use pesticides containing endocrine-disrupting chemicals and petrochemicals in the home [48]. DDT was one of the more commonly used pesticides and has well-documented epigenetic transgenerational effects [25, 49, 50].

We have several interesting findings. The Mother and Father clusters (see Figs. 2 and 3) generated similar results in the number of clusters, p-value, and time span except for the large, detected cluster encompassing the southwest counties. Maternal Grandmother clusters results show the same cluster pattern as the mother and father clusters. To determine if residential location remained the same between generations, an overlap analysis was conducted identifying the family member and shared residential location between clusters and ancestor generation. We found that less than 5% remained in the same residential location as the ancestor group.

Arguably, our most interesting findings are the paternal grandparent clusters with RR > 2.74. These clusters are at a sub-city scale in size and are highly compact in time and space. The clusters occurred in urban settings of their time, suggesting that the underlying factors may be associated more generally with the urban environment than with specific unique point sources of contamination. This is not to say that diagnostic bias in rural and urban areas has not occurred. Family members are also more likely to share the same space-time, so clusters may
### Table 2  Ancestor Space-time Cluster Results

| Relative | Developmental window | Cluster number | Time range       | Observed/expected | RR      | P-value  | Bonferroni correction | Area km² | Percent street location (%) | Cohort effect | Census rural/urban classifications |
|----------|----------------------|----------------|------------------|-------------------|---------|----------|------------------------|----------|-----------------------------|--------------|-----------------------------------|
| Mother   | Birth                | 1              | 1966–1995        | 1557/1326.20      | 1.31    | 0.0001   | 1.0E–7               | 2286     | 93                          | 542 → Cluster 4 | Urban                             |
|          |                      | 2              | 1959–1984        | 409/560           | 0.70    | 0.0001   | 1.0E–7               | 122      | 93                          | 0            | Rural                             |
|          |                      | 3              | 1972–1983        | 18/48             | 0.03    | 0.034    | 3.4E–5               | 93       | 0                           | 0            | Rural                             |
|          | Childhood            | 4              | 1955–2000        | 1272/1059         | 1.2     | 0.0001   | 4.0E–7               | 1633     | 93                          | 542 ← Cluster 1 | Urban                             |
| Maternal grandmother | Birth         | 5              | 1957–1975        | 203/140           | 1.49    | 0.0004   | 1.9E–5               | 226      | 91                          | 0            | Rural                             |
|          |                      | 6              | 1951–1961        | 68/119            | 0.55    | 0.0023   | 2.3E–6               | 408      | 91                          | 0            | Urban                             |
|          | Childhood            | 7              | 1940–1957        | 58/78             | 0.34    | 0.0003   | 3.0E–7               | 482      | 91                          | 53 → Cluster 8 | Rural                             |
|          | Adolescence          | 8              | 1960–1989        | 1/16              | 0.06    | 0.029    | 2.9E–5               | 940      | 100                         | 53 ← Cluster 7 | Rural                             |
| Maternal grandfather | Birth          | 9              | 1946–1973        | 711/583           | 1.36    | 0.0001   | 1.0E–7               | 3247     | 91                          | 3 → Cluster 10 | Rural/Urban                        |
|          | Childhood            | 10             | 1931–1983        | 696/597           | 1.32    | 0.0009   | 9.0E–7               | 2336     | 89                          | 3 ← Cluster 9 | Urban                             |
| Father   | Birth                | 11             | 1952–1994        | 2029/1796         | 1.27    | 0.0001   | 1.0E–7               | 4248     | 93                          | 431 → Cluster 13 | Urban                             |
|          | Childhood            | 12             | 1956–1981        | 614/757           | 0.77    | 0.0004   | 4.0E–8               | 25,943   | 93                          | 10 → Cluster 14 | Rural                             |
|          |                      | 13             | 1953–2002        | 899/749           | 1.31    | 0.0000   | 1.0E–7               | 1661     | 92                          | 431 ← Cluster 11 | Urban                             |
|          |                      | 14             | 1968–1987        | 212/291           | 0.70    | 0.0065   | 6.5E–6               | 14,733   | 92                          | 10 ← Cluster 12 | Rural                             |
| Paternal grandmother | Birth          | 15             | 1951–1957        | 24/8              | 2.74    | 0.002    | 2.0E–6               | 24       | 91                          | 0            | Urban                             |
|          |                      | 16             | 1956–1957        | 17/5.7            | 2.96    | 0.001    | 1.0E–6               | 8        | 91                          | 91%          | Urban                             |
|          |                      | 17             | 1953–1963        | 15/5.1            | 2.96    | 0.0049   | 4.9E–5               | 14       | 91                          | 0            | Urban                             |
|          |                      | 18             | 1952–1954        | 24/8.5            | 2.86    | 0.002    | 2.0E–6               | 132      | 91                          | 0            | Urban                             |
|          |                      | 19             | 1931–1969        | 805/702           | 1.28    | 0.004    | 4.0E–6               | 681      | 91                          | 0            | Urban                             |
| Paternal grandfather | Childhood       | 20             | 1935–1969        | 311/242           | 1.36    | 0.025    | 2.5E–5               | 98       | 89                          | 0            | Urban                             |

Statistical significance of each cluster was measured at $p < 0.05$ using Monte Carlo simulation.
reflect the clustering of genetic predispositions from clustering of family members. However, grandparents share fewer genes with grandchildren which suggests our paternal grandmother clusters and paternal cluster could be non-genetic factors. Because we have moved forward in time from grandparent-to-parent in our space-time cluster methodologies, it has not been possible to determine the level of relatedness between ASD proband children, as they have not been the focus of the study outside of pedigree building. This creates an opportunity to study the specific question of relatedness and genetic similarity of clusters in future work.

Both genetic and epigenetic changes may be possible mechanisms to explain how the environment can impact an ancestor, which may be transferred transgenerationally to a descendent. Transgenerational health outcomes from environmental exposures have been well established in animal studies where multiple generations of animals live and are carefully observed for changes in health patterns [25, 51, 52]. The same types of transgenerational observations in human populations are more difficult to observe as family location data with disease outcomes are not readily available, but they still exist. A study investigating persistent ionizing radiation exposure in grandparent generations, for example, found an increased incidence of low bone density in their young adult grandchildren [53]. Another notable example is the investigation into grandparent exposure to dioxin TCDD, an herbicide used in the Vietnam War as a chemical agent. Researchers found mutations that occurred in spermiogenesis that impacted the health of their progeny, including leukemias [54, 55]. Tabaco smoke exposure is well studied in humans and transgenerational effects are recognized [56].

Strengths and limitations

Strengths
The study has several strengths, most relating to the high data integrity and the richness of the records, allowing investigators to place individuals in pedigrees, and throughout space and time. The dataset allows us to link family members over space and time at different vulnerable developmental windows and has been key to identifying space-time clustering. The rich location data within the records provide sufficient information to include thousands of records. As a result, the analysis was based on a large number of ancestors of ASD cases starting with a very complete case ascertainment for case children/grandchildren born in Utah from 1989–2014 (n = 3957).

Using the unique linked pedigree and vast administrative data in the UPDB we were able to generate a large dataset of residential locations for both parents and grandparents at three critical developmental windows with a high level of completeness. The dates and residential locations used are based on a consistent and reliable source of information—birth certificates and medical records, with the majority of our addresses being home addresses (> 90%).

Additionally, we used only clinically diagnosed ASD case children to create our family pedigrees. While keeping our ASD cases defined by clinical diagnosis, we used a broad statewide dataset, as opposed to limiting the study to a specific county or regional jurisdiction. This decision was made to ensure the study included both rural and urban residential locations over space and time.

The study has several data limitations. The study includes Utah children only. The URADD dataset is specific to Utah and does not include any other person outside of the state. We omitted the sex of the case children when compiling the pedigrees. This will be completed for a future study when permissions are granted to include case children in the analysis. We did not have any information relating to adoption. Family pedigrees were generated based on birth certificate information. If a non-biological person was on a birth certificate, we would not have information indicating they are adopted or had adoptive parents. We lacked information on the relatedness of grandparents to each other. This can be addressed in future studies. Also, we did not have complete residential histories. Our study was limited to information in administrative records from URADD and UPDB. If a person moved and did not generate a record for that time we would not be aware of such moves. This omission, however, would likely serve to generate conservative (i.e., RR's biased toward 1) estimates of risk.

Future studies
Our understanding of possible transgenerational factors affecting the risk of ASD could be improved by other cluster analyses to corroborate these findings. In addition, analytical studies are needed to assess the relationships between environmental factors experienced by parents and grandparents and the likelihood that their descendent have ASD. Our cluster analysis results can be used to further study exposures of the temporal ranges identified, and at around the cluster locations identified which in so doing helps bridge the gap between transgenerational exposures and heritable health outcomes. Additionally, with our current results and family pedigrees we have compiled, we can further investigate the rural and urban locations of ASD case children and their location-where-diagnosed to determine if they maintained a rural or urban residence that matches their ancestor identified in clusters.
Given that little is known, and very little work has been done regarding transgenerational disease inheritance from environmental exposures, our space-time cluster study, using individual records, will add to the growing body of knowledge regarding this subject. The framework used and presented in this paper can be employed by any study looking for health effects from unmeasured ancestral space-time exposures.

Conclusion
Our study findings indicate that specific shared time and space of ancestors is associated with an increased likelihood of an ASD diagnosis in decedents. At this point, these results do not provide information that can be directly used to identify individuals at higher risk or provide other direct benefits to individuals with ASD. The results to provide some evidence of transgenerational risks and lays the foundation for future research to identify risk factors that can lead to increased risks of ASD and other adverse health outcomes across generations. We are currently examining the associations between a variety of environmental conditions during critical exposure windows of parents and grandparents and the risk of ASD in their progeny. Identifying and addressing such risk factors may lead to reduced risks for future generations. These implications are broad and need further investigating, but the time and space of interest and the family pedigrees of interest have been identified and can be studied further.”

Our strongest signal identified is from the paternal grandparent’s birth and childhood vulnerable developmental windows. Subdividing the data by maternal and paternal lineage revealed surprising results of the paternal grandparent clusters carrying the highest relative risk at statistically significant levels (P < 0.05), which is a possible signal for a transgenerational effect from birth and childhood exposures.

Abbreviations
ASD: Autism spectrum disorder; UPDB: Utah population database; URADD: Utah registry of autism and developmental disabilities.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12942-022-00313-4.

Additional file 1: Table S1. Overlap Analysis Results.

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Author contributions
RRS: Hypothesis formulation, analysis design, data acquisition, results interpretation, paper writing. AVB: Regulatory assistance for data acquisition, assistance in analysis design. KRS: Grant assistance for data acquisition, paper edits. NW: Analysis, interpretation, paper edit assistance. RM: Analysis interpretation assistance, paper edits. SB: Analysis interpretation assistance, paper edits. JV: Study design assistance, data results interpretation assistance, paper editing assistance. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from URADD and UPDB but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of URADD and UPDB.

Declarations
Ethics approval and consent to participate
Ethics approval for data on human subjects was obtained by the Utah Registry of Autism and Developmental Disabilities, the Utah Department of Health, the University of Utah Internal Review Board, and the Utah Resource for Genetic and Epidemiologic Research.

Consent for publication
The Utah Department of Health, the Utah Registry of Autism and Developmental Disabilities, the University Internal Revenue Board, and the University of Utah Resource for Genetic and Epidemiologic Research committee’s have reviewed and approved the data, data analysis, and paper for publication. IRB_00057455 RGE_00000781 Utah Department of Health and URADD approval # 513.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Geography, University of Utah, 260 Central Campus Dr #4625, Salt Lake City, UT 84112, USA. 2 Department of Psychiatry, University of Utah, 501 Chipeta Way, Salt Lake City, UT 84108, USA. 3 Pedigree and Population Resources, Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope Drive, Salt Lake City, UT 84112, USA. 4 Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah, USA. 5 Department of Geography, University of Utah, 537 W. 3900 S., Bountiful, UT 84010, USA.

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References
1. Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/ncbddd/autism/data.html. Accessed 3 Mar 2022.
2. https://www.cdc.gov/ncbddd/autism/addm-community-report/executive-summary.html. Accessed 5 July 2022.
3. Christensen DL, Maenner MJ, Bilder D, Constantino JN, Daniels J, Durkin MS, Fitzgerald RT, Kurzius-Spencer M, Pettygrove SD, Robinson C, Shennouda J. Prevalence and characteristics of autism spectrum disorder among children aged 4 years—early autism and development disabilities monitoring network; seven sites, United States, 2010, 2012, and 2014. MMWR Surveill Summ. 2019;68(2):1.
4. Edition F. Diagnostic and statistical manual of mental disorders. Am Psychiatric Assoc. 2013;21(21):591–643.
5. Gamess ED, Viscidi EW, Frederick AM, Nagpal S, Sanders SJ, Murtha MT, Schmidt M, Triche EW, Geschwind DH, State MW, Istrail S. Intellectual disability is associated with increased runs of homozygosity in simplex autism. Am J Hum Genet. 2013;93(1):103–9.
6. Chaste P, Leboyer M. Autism risk factors: genes, environment, and gene–environment interactions. Dialogues Clin Neurosci. 2012. https://doi.org/10.31887/DCNS.2012.
7. Dunaway KW, Islam MS, Coulson RL, Lopez SJ, Ciernia AV, Chu RG, Yasui DH, Pessah IN, Lott P, Mordauta C, Meguro-Horike M. Cumulative impact of polychlorinated biphenyl and large chromosomal duplications on DNA methylation, chromatin, and expression of autism candidate genes. Cell Rep. 2016;17(1):3035–48.

8. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lutschi P. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry. 2011;68(1):1095–102.

9. Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry. 2005;46(9):963–71.

10. Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Bryson S, Carver LJ, Constantino JN, Dobbins K, Hutman T. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. Pediatrics. 2011;128(3):e88–95.

11. Taylor MJ, Rosenquist MA, Larsson H, Gillberg C, D’Onofrio BM, Lichtenstein P, Lundstrom S. Epigenetics of autism spectrum disorders and autistics traits over time. JAMA Psychiatry. 2020;77(9):9:536–43.

12. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. JAMA. 2014;311(17):1770–7.

13. Bai D, Marrus N, Yip BH, Reichenberg A, Constantino JN, Sandin S. Inherited risk for autism through maternal and paternal lineage. Biol Psychiatry. 2020;88(6):480–7.

14. Brandler WM, Antaki D, Gupral M, Kleiber ML, Whitney J, Maile MS, Hong O, Chapman TR, Tan S, Tandon P, Pang T. Paternally inherited cis-regulatory structural variants are associated with autism. Science. 2018;360(6366):327–31.

15. Dickerson AS, Rahbar MH, Han I, Bakian AV, Bilder DA, Harrington RA, Petteway S, Durkin MA, Kirby RS, Wingate MS, Tian LH. Autism spectrum disorder prevalence and proximity to industrial facilities releasing arsenic, lead and mercury. Sci Total Environ. 2015;1(536):245–51.

16. Dickerson AS, Rahbar MH, Bakian AV, Bilder DA, Harrington RA, Petteway S, Kirby RS, Durkin MA, Han I, Moyé LA, Pearson DA. Autism spectrum disorder prevalence and associations with air concentrations of lead, mercury, and arsenic. Environ Monit Assess. 2016;188(1):1–5.

17. Gong T, Dalman C, Wicks S, Dal H, Magnusson C, Lundholm C, Almqvist C, Pershagen G. Perinatal exposure to traffic-related air pollution and autism spectrum disorders. Environ Health Perspect. 2017;125(5):119–26.

18. Grindler NM, Vanderlinden L, Karkhikar R, Kannan K, Teal S, Polotsky AJ, Powell TL, Yang W, Janssens T. Exposure to phthalate, an endocrine disrupting chemical, alters the first trimester placental methylome and transcriptome in women. Sci Rep. 2018;8(1):1–9.

19. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, Einarson J. Prenatal exposure to airborne pollutants in the San Francisco Bay area. Environ Health Perspect. 2006;114(8):1287–92.

20. Skinner MK, Guerrero-Bosagna C. Environmental signals and transgenerational epigenetics. Epigenomics. 2009;1(1):111–7.

21. Kubota T, Mochizuki K. Epigenetic effect of environmental factors on autism spectrum disorders. Int J Environ Res Public Health. 2016;13(5):504.

22. Breton CV, Marutani AN. Air pollution and epigenetics: recent findings. Front Cell Dev Biol. 2014;2(1):35–40.

23. Felsenfeld G. A brief history of epigenetics. Cold Spring Harb Perspect Biol. 2014;6(1):a018200.

24. Antezana L, Scarpa A, Valdespino A, Albright J, Richey JA. Rural trends and farm status report. https://data2.nhgis.org/main. Accessed 20 July 2021.

25.觚田つかましり, 木村敬一, 隈田慎之助, 瀬戸栄一, 木村貴之, 田村康之, 長谷川正明, 佐藤茂, 藤本直之, 大橋章子. 筆者の研究が示唆する隔代隔代影響と遺伝子変異. Dev Biol. 2011;4(Suppl):3451–5.

26. Perera FP, Rauh V, Whathy RM, Taiy WW, Tang D, Diaz D, Hoepner L, Barr D, Tu YH, Camann D, Kinney P. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect. 2006;114(8):1287–92.

27. Skinner MK, Ben Maamar M, Sadlier-Riggleman I, Beck D, Nilsson E, McImnire M, Kukulov P, Xie Y, Tang C, Yan W. Alterations in sperm DNA methylation, non-coding RNA and histone retention associate with DDT-induced epigenetic transgenerational inheritance of disease. Epigenetics Chromatin. 2018;1(1):1–24.

28. Sahar L, Foster SL, Sherman RL, Henry KA, Goldberg DW, Stinchcomb DG, Bauer JE. GSCience and cancer: state of the art and trends for cancer surveillance and epidemiology. Cancer. 2019;125(5):2544–60.

29. Skate SL, Yu H, Bombom LS. A space-time GIS approach to exploring large individual-based spatiotemporal datasets. Trans GIS. 2008;12(4):425–41.

30. Bitto A, Pizzorno G, Irrea N, Gallo F. Squadrato F. Epigenetic modifications due to heavy metals exposure in children living in polluted areas. Curr Genomics. 2014;15(6):464–8.

31. Skinner MK. What is an epigenetic transgenerational phenotype? F3 or F2? Reprod Toxicol. 2008;25(1):2–6.

32. Zhang C, Sun B. Sex biased gene expression profiling of human brains at major development stages. Sci Rep. 2016;6(1):1–9.

33. Kulldorff M, Heffernan R, Hartman J, Assunção R, Mostashari F. A space-time permutation scan statistic for disease outbreak detection. PLoS Med. 2005;2(13):e59.

34. Nordsborg RB, Sloan CD, Shahid H, Jacquez GM, De Roos AJ, Gerhan JR, Cozen W, Severson R, Ward MH, Morton L, Raaschou-Nielsen O. Investigation of spatio-temporal cancer clusters using residential histories in a case-control study of non-Hodgkin lymphoma in the United States. Environ Health. 2015;14(1):1–8.

35. Sloan CD, Nordsborg RB, Jacquez GM, Raaschou-Nielsen O, Meliker JR. Space-time analysis of testicular cancer clusters using residential histories: a case-control study in Denmark. PLoS ONE. 2015;10(3):e0120285.

36. Baumgartner R, Somoraji R, Summers R, Richter W, Ryner L, Jarmasz M. Resampling as a cluster validation technique in MRI. J Magn Reson Imaging. 2000;11(2):228–31.

37. Koenig WD. Spatial autocorrelation of ecological phenomena. Trends Ecol Evol. 1999;14(1):22–6.

38. The U.S. Census Bureau (1960, 1970, 1980, 1990, 2000) Urban, rural, and farm status report. https://data2.nhgis.org/main. Accessed 20 July 2021.

39. Antziana L, Scarpa A, Valdespino A, Albright J, Richey JA. Rural trends in diagnosis and services for autism spectrum disorder. Front Psychol. 2017;20(8):590.

40. Lauritsen MB, Astrapu A, Pedersen CB, Obel C, Schendel DE, Schieve L, Yeargin-Allsopp M, Parner ET. Urbanicity and autism spectrum disorders. J Autism Dev Disord. 2014;44(2):394–404.

41. Pembrey M, Saffery R, Bygren LO. Human transgenerational responses to early-life experience: potential impact on development, health and biomedical research. J Med Genet. 2014;51(9):563–72.

42. Biehler DD. Permeable homes: A historical political ecology of insects and pesticides in US public housing. GeoForum. 2009;40(6):1014–23.

43. Kabasenche WP, Skinner MK. DDT, epigenetic harm, and transgenerational environmental justice. Environ Health. 2014;13(1):1–5.

44. Maamar MB, King SE, Nilsson E, Beck D, Skinner MK. Epigenetic transgenerational inheritance of parent-of-origin allelic transmission of outcross pathology and sperm epimutations. Dev Biol. 2020;458:106–19.

45. Lombó M, Fernández-Diez C, González-Royo S, Navarro C, Robles V, Herranz MP. Transgenerational inheritance of heart disorders caused by paternal bisphenol a exposure. Environ Pollut. 2015;1(206):667–78.

46. Shukla A, Bunkar N, Kumar R, Bhargava Tiwari Chaudhury Goryacheva ARNY, Mishra PK. Air pollution associated epigenetic modifications:
transgenerational inheritance and underlying molecular mechanisms. Sci Total Environ. 2019;15(656):760–77.

53. Ivanova R, Goremykina M, Rakhybpakov T, Glushkova N, Kryykabayeva S, Grijbovski AM. High prevalence of low bone mineral density in young adults whose grandparents were exposed to ionizing radiation at the Semipalatinsk Nuclear Test Site Kazakhstan. Andrej Grijbovski. European J Public Health. 2014. https://doi.org/10.1093/eurpub/cku166.102.

54. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. USA: San Francisco; 2012.

55. Giuliani C, Biggs D, Nguyen TT, Marasco E, De Fanti S, Garagnani P, Le Phan MT, Nguyen VN, Luiselli D, Romeo G. First evidence of association between past environmental exposure to dioxin and DNA methylation of CYPIA1 and IGF2 genes in present day Vietnamese population. Environ Pollut. 2018;1(242):976–85.

56. Ortega-Garcia JA, Martin M, Lopez-Fernandez MT, Fuster-Soler JL, Donat-Colomer J, Lopez-Ibor B, Claudio L, Ferris-Tortajada J. Transgenerational tobacco smoke exposure and childhood cancer: an observational study. J Paediatr Child Health. 2010;46(6):291–5.

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