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Short Communication

Investigating the causes of birth defects.

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Abstract

Background: Understanding and investigating the causes of birth defects is a critical approach toward the findings and development of helpful treatments and diagnostic strategies to overcome the issue of birth defects. We aim to investigate birth defects' causes by identifying the most common abnormal genes found in an inheritance pattern. Collecting genetic causes of the most common birth defects found in Pakistan and searching the link between birth defects and other harmful diseases.

Methodology: The birth defects data is systematically gathered and critically analyzed to assess the role of insertions and deletions as the causative agents. Analysis was conducted on genomic data to investigate the genetic causes of congenital abnormalities.

Results: The most common birth defects, namely neural tube defect (spina bifida), Facial palate (cleft/lip palate), heart defects (atrial septal defect, ventricular septal defect, tetralogy of Fallot), deletion syndrome, and laryngomalacia caused by the main problematic genes namely MTHFR, MEIS2, TBX1, and NKX2-5. The results show that about eighty-six percent (86%) of gene variants overlap completely with the defective genes transcript, including both insertions/gain and deletions/loss.

Conclusion: Identification of the main genes which are involved in most of the common birth defects highlights the major twelve genes, namely LMNA, MTHFR, POMC, TTN, SLC25A13, FGFR3, GCH1, TBX1, MEIS2, NKX2-5, GATA4, and GATA6.

Keywords

Birth Defects Data, Copy Number Variation, Loss of DNA, Causes, Inheritance, Freely Accessible Data.

Introduction

WHO reported that more than 303,000 infants are born with severe congenital abnormalities yearly and die within four weeks of birth[1,2]. About 3-6 percent of defects are life-altering birth defects[1]. In Pakistan, the neonatal mortality rate (NMR) is 46 deaths per 1,000 live births. The leading causes of these deaths can be seen in chart 1, and Preterm birth complications are Pakistan's leading cause of neonatal deaths[3]. The most common birth defects found in Pakistan are related to the urogenital system, eye, musculoskeletal system, body wall defects, oral cavity, central nervous system, and others that are less common are related to the gastrointestinal tract, cardiovascular system, and those related to ear, nose, and throat[4]. Birth defects can be classified as structural defects or functional and developmental defects. The Structural defect affects the formation of specific body parts. For example, congenital heart disease, or a congenital heart defect, is a heart abnormality present at birth, e.g., ventricular septal defect (VSD) caused by the novel mutation of the GATA4 gene[5], in which one ventricle is underdeveloped and has a mini hole and only the other one is performing the functions[6]. Functional or developmental birth defects are found in a body part or system which is not working properly[7]. These defects often affect the child's intelligence or development. Functional or developmental birth defects are related to metabolic and sensory/nervous system problems.

Birth defects are caused due to any single sporadic event during the fetus's development. It can be syndromic, nonsyndromic, inherited, or non-inherited[8]. The genetic cause of birth defects includes irregular gene mutations causing abnormalities in the morphological pathways[9]. Some birth defects are the reason by multiple factors, such as the interaction between genes and the prenatal environment[10]. Later during the organogenesis phase, disruption takes place, which causes substantial structural anomalies, i.e., ventral body wall defect (Gastroschisis), neural tube defect (Spina bifida), any facial cleft (Lip palate), and heart valve formation[11]. Inherited birth defects can be caused due to chromosomal mutations, genetic mutations like single gene defects, or dominant or recessive inheritance[12]. Chromosomal mutations can lead to early fetal malformations, pregnancy loss, or stillbirth[13]. There can be different types of chromosomal changes, namely; deletions, duplications, translocations, and inversions which could cause numerous birth defects[14]. Copy number variation, an example of structural chromosomal abnormality, occurs due to the deletion, duplication, or insertion of chromosomes[14]. Copy number variants (CNVs) are discussed further in the 2.3 section. Genes perform their functions in pairs, and random alterations in any of them will cause genetic mutation and lead to congenital abnormalities[15]. These mutations can be of different types i.e. Autosomal recessive and Autosomal dominant inheritance patterns. Non-inherited birth defects are the ones that are caused by unexpected mutations due to any external factor influencing the fetus's development, involving environmental exposure to some chemicals, radiation, or smoke from cigarettes. These non-inherited pathways are observed rarely in only 1% of all human malformations.

Copy number variation is caused by microdeletion or microduplication, which is either loss or gain of the stretch of DNA compared to the reference of the human genome[16]. In a human genome, a gene contains some specific copy number, e.g., one, three, etc.[17]. While some of the gene's copy number remains constant, some are variable too, depending on each individual.

A wide range of CNV sometimes causes the addition and deletion of genetic material, creating trouble in the sub-chromosomal scale that leads to a change in phenotype, which causes disease[17]. Several mechanisms combine to cause a change in the phenotype of a healthy individual through copy number variation. For example, insertions could cause over-expression or a high gene dosage, which may result in a defective phenotype[17]. Copy number variants binding with some regulatory elements indirectly cause gene expression changes. For instance, deletion/loss of a regulatory element could affect the dosage-Sensitive gene performance (Figure 2) will lower/higher the gene expression than normal[17]. We aim to investigate

birth defects' causes by identifying the most common abnormal genes found in an inheritance pattern. Collecting genetic causes of the most common birth defects found in Pakistan and searching the link between birth defects and other harmful diseases.

Methodology

The main idea of the present study was to gather the birth defect data of the past 25 years and search for the relationship between the genes causing those birth defects. The birth defects data was gathered together with the help of different birth defect research articles, databases, and organizations, including Online Mendelian inheritance in man (OMIM), National center for biotechnology information (NCBI), Human phenotype ontology (HPO), Pediatric disease annotations and medicines (PEDAM), MEDLINE database of references and abstracts on life sciences and biomedical topics (PUBMED), Science Direct, Springer Nature, Wiley online library and Pakistan genetic mutation database (PGMD).

All the genomic and copy number gene variant data is retrieved from the Ensembl genome browser. Data used is first converted into GRCh38.p13 updated the human genome version, also called hg38, through the Lift Genome Annotations tool. The extracted genomic data file contains Gene stable ID, stable Transcript ID, Chromosome/scaffold number, Gene name, Gene start position (bp), and Gene end position (bp) in six columns. The extracted copy number gene variant data file contains chromosome number, gene variant starting position (bp), gene variant ending position (bp), copy number variation (loss/gain), gene name, Gene start position (bp), Gene end position (bp), Gene stable ID, stable Transcript ID, transcript start position (bp), transcript end position (bp), gene transcript count.

Any data showing any sort of inappropriate repetitive pattern is removed from the file and the data processing functions are performed through LINUX CentOS 8. A total of five hundred and five defective genes from the collected birth defect databases are then overlapped with the extracted copy number gene variant data file through the bedtools intersect command for further analysis.

Results

After examining the whole birth defects data, major genes are identified, namely GATA4, GATA6, POMC, GCH1, SLC26A13, TTN, FGFR3, NKX2-5, LMNA, MEIS2, TBX1, MTHFR (shown in the bar chart 3) that are mainly involved in the number of birth defects. These twelve genes are causing the highest number of birth defects, where LMNA, MTHFR, and POMC lead the list.

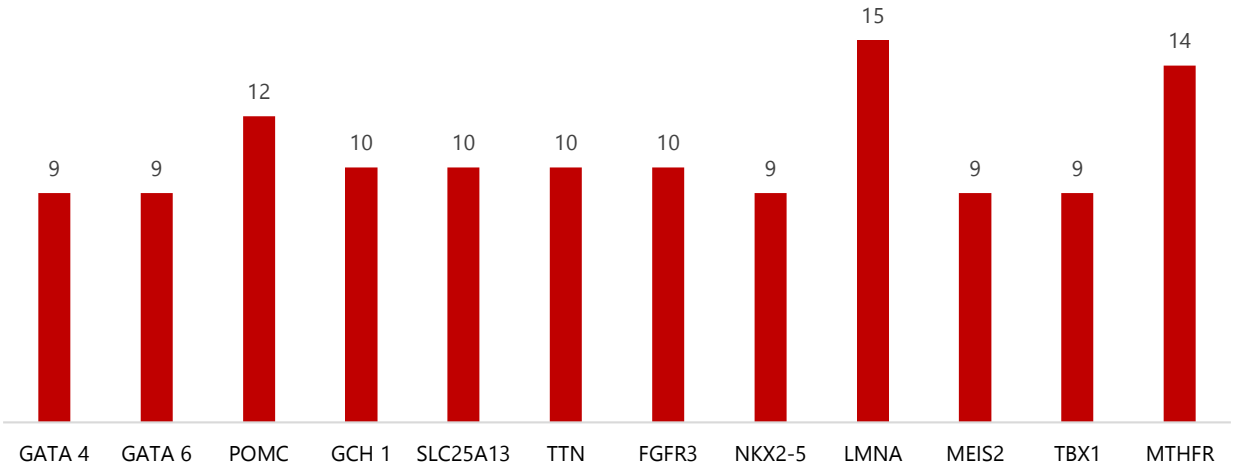

Figure 1: Major genes involved in the birth defects based on the collected birth defects data.

After identifying the major problematic genes, birth defects interrelated with these particular defect-causing genes are investigated, highlighting the most common birth defects through a Venn diagram shown in figure 2.

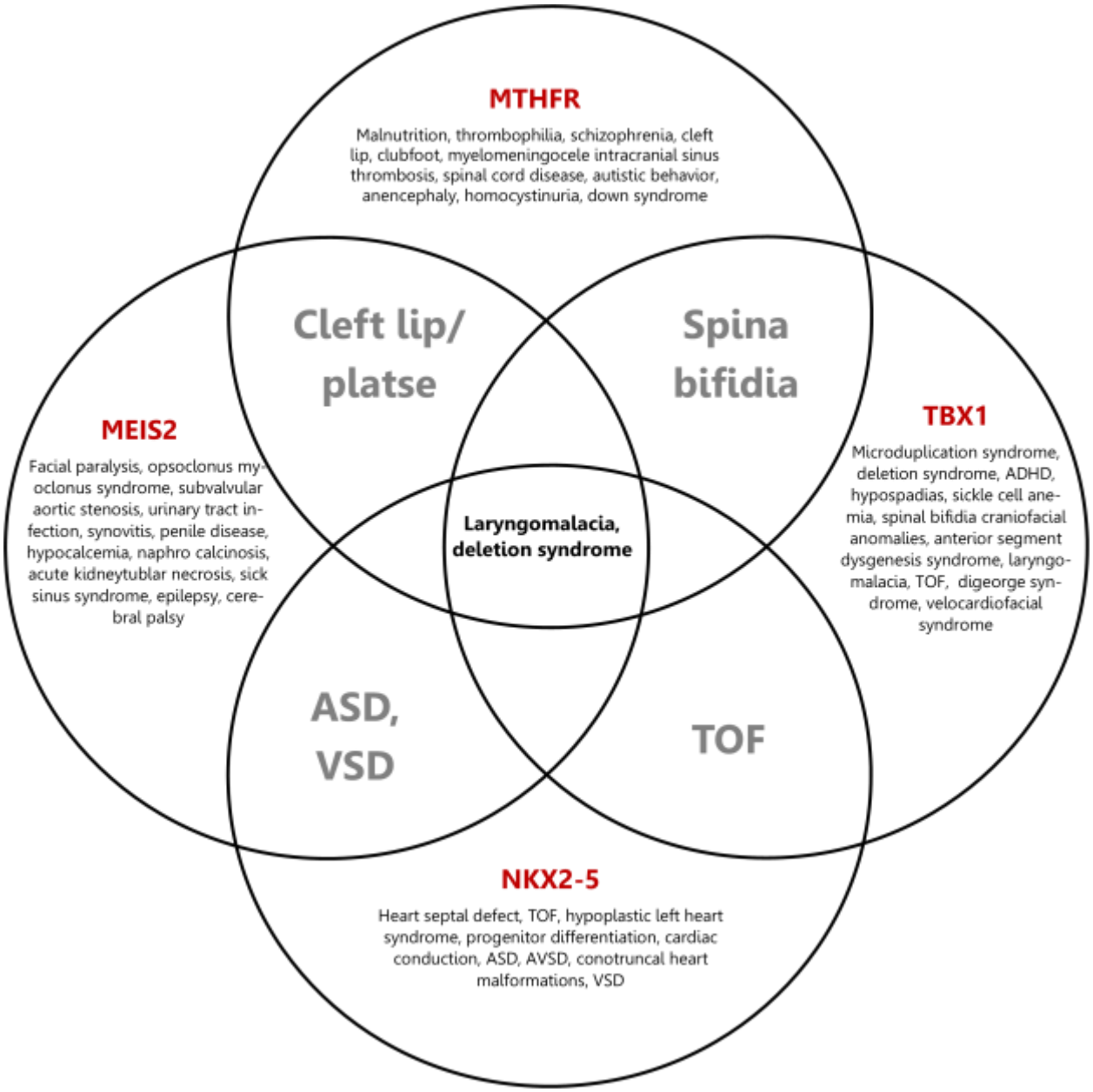

Figure 2: Venn diagram of major genes involved in interrelated birth defects.

The Venn diagram clearly shows the most common birth defects, namely neural tube defect (spina bifida), Facial palate (cleft/lip palate), heart defects (atrial septal defect, ventricular septal defect, and tetralogy of Fallot), deletion syndrome, and laryngomalacia caused by the main problematic genes namely MTHFR, MEIS2, TBX1, and NKX2-5. As shown in Table 1, the conserved region found in these genes showed a random pattern

of occurrence. We have categorized genes into highly conserved regions, low conserved regions, and medium conserved regions.

Table 1: Conserved regions found in genes.

Genes	Conserved Region (Introns)
MTHFR *	Low
TBX1 *	Medium
MEIS2 *	High
NKX2-5 *	Low
FGFR3 *	Medium
TTN **	Very low
LMNA **	Medium
GCH1 **	Medium
SLC25A13 **	High
POMC *	Very low
GATA6 *	High
GATA4 *	High

* involved in both inherited and non-inherited birth defects

** involved in inherited birth defects.

The results show that about eighty-six percent (86%) of gene variants overlap completely with the defective genes transcript, including both insertions/gain and deletions/loss. From the complete analysis of those gene variants, deletion/ loss of genetic information is found in a great adequate amount, highlighting the harmful effect on the human genome causing most of the deadly congenital birth defects. After the deletion/loss of genetic information, the affected gene performance shows the cellular response, which reflects the function of that deleted gene. These deletions, where the function of a dosage-sensitive gene is completely altered, are very harmful and disturb the whole genetic function of that specific gene.

Discussion

Congenital birth defects may be caused due to parental genetics, lifestyle, exposure to chemicals and rays or certain medications, infectious and nutritional factors during pregnancy, or maybe a combination of any of these factors, which can lead to problematic chromosomal mutational changes[18]. Birth defects can be fatal or non-fatal, and in both cases, they cause a long-term negative impact on individuals, families, the health sector, and society[18]. According to WHO, the most commonly found birth defects are neural tube, heart, and Down's syndrome. The cause of these defects is also due to less efficient resource management[18]. Identifying the exact cause of a congenital abnormality may be difficult, but we can reduce the risks of having these anomalies by taking some beneficial measures. Due to poor maternal health linked to poverty, congenital defects can be prevented with the help of proper nutritional supplements provided to the mother by a clinician[18]. Research shows that several birth defects, majorly neural tube defects, are caused by a deficiency of folic acid in the early stages of development during pregnancy[19].

In the birth defects datasheet, each birth defect is linked with its gene and also with the other defects which may be caused due to that particular defective gene. The genetic information of a parent's DNA passing to a child's physical appearance is called the genotype-phenotype relationship[20-22]. This genotype-phenotype interrelation is shown through a Venn diagram in Figure 2. The genotype-phenotype relationship highlights numerous defect/disease-causing genes and helps us to identify the inheritance pathway of the defect/disease[22]. We can see clearly from the

Venn diagram that all these majorly involved genes are causing birth defects at different organ levels and not for any specific organ or body part.

By analyzing the conserved regions of the main genes involved in the common birth defect, it was clear that the main problematic genes could not be found at any common chromosomal location, which shows a random pattern of occurrence[23]. Several birth defects are caused due to the copy number variation[24]. The main reason behind the cause of birth defects due to either the loss or gain of genetic information is not found yet. Copy number variation, i.e., deletion/loss of genetic information, contributes greatly to causing congenital abnormalities and many harmful diseases[25].

This study would aid future research, including molecular diagnosis, disease resistance, and treatment strategies. Dietary nutritional supplements also play a great role in the early developmental stage of a healthy child. It is to be assured that a pregnant woman should have adequate access to a healthy diet along with proper nutritional supplements, i.e., folic acid and iodine[18]. They should avoid any alcoholic or inadequate drug resources and smoke. A healthy environment free from harmful chemicals/rays should be provided to both baby and mother. All these factors combined will greatly impact reducing the risks of birth defects in Pakistan and worldwide.

Conclusion

Identification of the main genes which are involved in most of the common birth defects highlights the major twelve genes, namely LMNA, MTHFR, POMC, TTN, SLC25A13, FGFR3, GCH1, TBX1, MEIS2, NKX2-5, GATA4, and GATA6. The findings related to copy number variation provide valuable insights and different clues to further investigate the deletions/losses of genetic material that will target reducing the risks of having birth defects early at the developmental stage.

Conflicts of Interest

The authors declare no conflicts of interest.

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