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Research Article

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Genotype-phenotype characteristics of β thalassemia children in the Gaza Strip, Palestine

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Abstract

Background

β-Thalassemia is a public health problem in the Gaza Strip, Palestine. The present work is aimed to determine any association between β-Thalassemia mutations and the phenotypes of Gazian patients.

Methods

Blood samples were collected just before scheduled blood transfusion from 53 β-thalassemic children who are already characterized for the causative mutation. Blood samples were collected also from 53 apparently healthy children of the same sex and age range. Complete blood count and biochemical tests were performed.

Results

Sixty-six percent (66.0%) of the β-thalassemic patients are receiving blood transfusions every 2-3 weeks. Splenectomized thalassemic patients represented only 7.5% of the cases. Significantly severe anemic presentations, remarkable thrombocytosis and leukocytosis were seen in the thalassemic patients. The biochemical characteristics showed significantly deteriorated liver and kidney function tests, except for urea. Homozygosity was reported in more than half of the patients. Some significantly different hematological and biochemical characteristics were reported among different genotypes.

Conclusion

It was concluded that, in addition to the previously reported molecular heterogeneity of β-thalassemic mutations in the Gaza Strip, deteriorated hematological and biochemical profiles were seen in the β-thalassemic patients, with possible correlation to genotype; this requires a more appropriate management protocol for those patients, especially with the severe mutation.

Keywords

β-thalassemia; Children; Molecular; Biochemical and hematological parameters; Gaza strip

Introduction

Thalassemias are considered one of the most common known hereditary blood disorders in mankind, quantitatively affecting the synthesis of human hemoglobin. At least 60,000 severely affected individuals are born every year. Thalassemias have been encountered in practically every racial group and geographic location in the world; however, they are most common among individuals originating from tropical and subtropical regions [1]. Thalassemias are classified based on the particular globin chain(s) that are produced in a reduced amount, so the main types of this inherited disorder which have been defined are α, β, δβ, δ, γδ β, and εγδβ thalassemias [2,3]. Although α- and β-thalassemias are the commonest types of thalassemia, the most important genetic variety of thalassemia is β-thalassemia, which is caused by impaired production of β-globin chain types, causing severe transfusion-dependent anemia, with significantly poor quality of life and diminished life expectancy in the homozygous and compound heterozygous states [4]. More than 400 different mutations have been reported and identified in the β globin (*HBB*) gene which are responsible for the development of the β-thalassemia [5]. Most types of β-thalassemia are due to point mutations, and large deletion mutations are found in rare cases [6,7]. The severity of clinical syndromes likely depends on the type of mutation in the *HBB* gene, and previous studies of other populations have revealed relationships between hematological/clinical phenotype and the type of β-thalassemia mutation [8-12]. Therefore, we designed the present work to explore the molecular, biochemical and hematological aspects of β-thalassemic children aged 5-12 years in the Gaza Strip, where more than 325 patients have been diagnosed with β-thalassemia major, as well as to investigate any genotype/phenotype associations which could be used to improve management protocols, such as blood transfusions and iron chelation, for these patients.

Material and Methods

All β-thalassemic, unrelated children aged 5-12 years old, registered at public hospitals in Gaza City who are currently being transfused and managed for the clinical symptoms and manifestations of the disease were considered as potential subjects for the present study. Our study included 53 transfusion-dependent β-thalassemic children (27 boys and 26 girls), whose causative mutations had been identified as mentioned in our previous study Sirdah et al. [13] and 53 apparently healthy children who served as a control group. The cases and controls were age and sex matched. Official approvals were obtained from the Helsinki Committee at the Palestinian Ministry of Health, and the Palestinian Thalassemia Center permitted participation in the study by the thalassemic children after their legal guardians' acceptance. One parent of each child signed the consent form.

Data were collected via questionnaire and from laboratory investigation of blood samples for biochemical and hematological parameters. Blood withdrawal of the β-thalassemic children was performed just before a scheduled blood transfusion. Five (5) ml of venous blood were collected from each subject (cases and controls). The collected blood was divided equally (2.5 ml) into K_3-EDTA tubes to perform complete blood count using a Cell Dyne 1700 electronic

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Table 1: General characteristics of the study groups.

Character	Patients n=53	Controls n=53	Statistics and P-value
Age (year) *Mean ± SD*	9.1 ± 2.2	8.8 ± 1.9	Independent t-test 4.81
95 % CI	8.5-9.7	8.3-9.3	
Sex			χ^2 test 0.846
Males	27 (50.9%)	29 (54.7%)	
Females	26 (49.1%)	24 (45.3%)	
Parents Consanguinity			χ^2 test 0.001
1st degree	38 (71.7%)	1 (1.9%)	
2nd degree	6 (11.3%)	2 (3.8%)	
Non relatives	9 (17.0%)	50 (94.3%)	

Table 2: General and some clinical characteristics of the patients.

	Number	Percentage
Blood transfusion		
2-3 weeks	35	66.0
4-5 weeks	17	32.1
More than 5 weeks	1	1.9
Iron chelation		
subcutaneous pump	24	45.3
Intramuscular infusion	22	41.5
Intravenous infusion	5	9.4
Oral (EXJADE)	2	3.8
Splenectomy		
Yes	4	7.5
no	49	92.5
Thalassemic brothers/sisters		
0	18	34.0
1	22	41.5
2	12	22.6
4	1	1.9

Table 3: Hematological characteristics of the study groups.

Parameters	Patients n=53	Controls n=53	P-value
	Mean ± SD	Mean ± SD	
WBC X 10^9/L	11.5 ± 12.0	7.1 ± 2.1	0.009
RBC X 10^{12}/L	3.3 ± 0.5	4.6 ± 0.4	<0.001
Hb (g /dL)	8.0 ± 1.0	11.4 ± 0.8	<0.001
HCT (%)	25.1 ± 3.2	36.5 ± 2.7	<0.001
MCV (fl)	75.9 ± 7.3	79.5 ± 4.4	0.003
MCH (pg)	24.1 ± 2.3	24.7 ± 2.2	0.148
MCHC (g /dL)	31.8 ± 0.7	31.1 ± 1.2	0.001
PLT 10^9/L	370.7 ± 152.9	284.8 ± 65.2	<0.001
RDW %	21.6 ± 10.9	15.3 ± 2.7	<0.001

WBC: White Blood Cells; **RBC:** Red Blood Cells; **Hb:** Hemoglobin; **HCT:** Hematocrit; **MCV:** Mean Corpuscular Volume; **MCH:** Mean Corpuscular Hemoglobin; **MCHC:** Mean Corpuscular Hemoglobin Concentration; **PLT:** Platelets Count; **RDW:** Red Blood Cell Distribution Width.

counter (Sequoia-Turner Corporation, California, USA) and serum tubes to determine aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin, urea, creatinine, uric acid, total protein, albumin, globulins, serum ferritin, serum calcium, and serum phosphorus, according to the available commercial kits.

The data were tabulated, encoded and statistically analyzed using the IBM SPSS Statistics (version 17, IBM Corporation, Somers, NY). The following statistical tests were performed aiming at description, identification of significant relationship, and differences between study items, variables and parameters. These tests are: Chi square test, Z-test, independent-samples t-test, and one-way analysis of variance (ANOVA). P values were two sided, and $P < 0.05$ was considered to indicate statistical significance.

Table 4: Biochemical characteristics of the study groups.

Parameters	Patients n=53	Controls n=53	*P*-value
	Mean ± SD	Mean ± SD	
ALT U/L	54.3 ± 50.0	17.4 ± 15.2	< 0.001
AST U/L	61.1 ± 36.8	27.9 ± 6.1	< 0.001
Urea mg/dL	23.5 ± 6.2	23.7 ± 5.8	0.871
Creatinine mg/dL	0.45 ± 0.08	0.54 ± 0.10	< 0.001
Uric acid mg/dL	4.2 ± 1.0	3.6 ± 0.8	0.001
Total Bilirubin mg/dL	1.2 ± 0.8	0.7 ± 0.1	< 0.001
Direct Bilirubin mg/dL	0.44 ± 0.40	0.26 ± 0.09	0.001
Total protein g/dL	6.4 ± 0.6	7.0 ± 0.4	< 0.001
Albumin g/dL	4.2 ± 0.3	4.7 ± 0.3	< 0.001
Globulins g/dL	2.1 ± 0.5	2.3 ± 0.3	0.061
Ferritin ng/mL	3231.0 ± 1560.5	46.8 ± 23.1	< 0.001
Calcium mg/dL	9.2 ± 0.6	9.7 ± 0.7	< 0.001
Phosphorous mg/dL	4.8 ± 0.8	4.7 ± 0.6	0.396

Results

The general characteristics of the study groups are outlined in Table 1. A remarkable and a significant difference was reported in the parents' consanguinity of the two groups. About 71% of the β-thalassemia major children parents are 1st degree cousins, compared to the control group where the percentage was less than 2.0%. Also, the percentage of 2nd degree consanguineous marriages in the thalassemic patient group was significantly higher than that of the control group, 11.3 and 3.8%, respectively.

General and clinical characteristics of the patients are summarized in Table 2. The majority (66.0%) of the thalassemic patients are receiving a blood transfusion each 2-3 weeks, with nearly half withdrawing overloaded iron through subcutaneous pumps (desferrioxamine mesilate (Desferal®)) and 41.5% through intramuscular infusion, while the newly approved oral iron chelator (deferasirox Exjade®) is used by only 3.8% of the patients. The presence of other thalassemic patients within the same family (i.e., brothers or sisters) is striking, with 66.0% of the current patients having other thalassemic brothers and/or sisters, who were excluded to rule out bias.

CBC parameters (Table 3) and indices measured in the present work revealed significant differences between patients and controls, except for MCH. Severe anemic presentations were seen in patients as compared to controls. In addition, significantly remarkable thrombocythemia and leukocytosis were reported in patients compared to controls. None of the hematological parameters or their related indices showed significant variations between males and females.

Significantly deteriorated liver and kidney functions tests, except for urea, were found in patients as compared to controls (Table 4). The protein contents, i.e., total protein, albumin, and globulins, were significantly reduced in patients as compared to control group. Moreover, there was a significant iron increase, leading to iron overload, in patients as compared to controls, with serum ferritin levels of 3231.0 ± 1560.5 ng/mL vs. 46.8 ± 23.1 ng/mL, respectively.

Table 5: Pearson coefficient for significant Correlations among patients" hematological and biochemical variables.

	Pearson correlation coefficient (r)	P-value
PLT vs WBC	0.606	0.001
PLT vs Hct	- 0.325	0.018
PLT vs Hb	- 0.320	0.02
Ferritin vs ALT	0.330	0.017
Ferritin vs AST	0.322	0.02
Ferritin vs Direct Bilirubin	-0.331	0.015
Ferritin vs Creatinine	0.296	0.033
Ferritin vs Uric acid	0.316	0.023
ALT vs Calcium	0.281	0.041
AST vs Calcium	0.276	0.045

Table 6: Genotype of patients according to the identified variants.

Genotype	Number	Frequency
Homozygous IVS-I-110	11	20.8
Homozygous CD39	7	13.2
Homozygous IVS-I-1	5	9.4
Homozygous IVS-I-6	3	5.7
Homozygous CD37	3	5.7
Subtotal	29	54.8
Double heterozygous	8	15.1
One variant identified	5	9.3
Unidentified	11	20.8
Total	**53**	**100**

Although serum calcium level was significantly reduced in patients compared to controls, no significant differences were reported in phosphorus levels. None of the biochemical tests showed variations between males and females. Pearson coefficient for significant correlations among patients" hematological and biochemical variables are presented in Table 5 which revealed significant correlations of PLT count with WBC count, Hb, Hct; of serum ferritin with ALT, AST, direct bilirubin, creatinine, uric acid; and of ALT and AST with calcium.

Table 6 presents the genotypes of patients according to the identified *HBB* variants, more than half (54.8%) of the patients showing a homozygous genotype. Homozygotes for the IVS-I-110 mutation represented 20.8% of patients, while homozygotes for the CD39 mutation and the IVS-I-1 mutation represented 13.2% and 9.4%, respectively. Double heterozygotes for two different mutations constituted 15.1% of the patients. The remaining patients' samples (16/53) were either semi-identified (5/53) or unidentified (11/53).

The hematological (Table 7) and biochemical (Table 8) characteristics according to patients' genotype were assessed and compared. Patients homozygous for the IVS-I-6 variant exhibited significantly different hematological characteristics compared to other genotypes, i.e., the highest RBC count, lowest MCV, lowest MCH and highest PLT count; however, no significant differences were reported for the other genotypes. On biochemical tests, patients homozygous for IVS-1-110 showed considerably deteriorated liver function tests in terms of ALT and AST, while those homozygous for IVS-1-6 showed a high serum urea concentration as compared to other genotypes. No significant differences were found between the different genotypes regarding creatinine, total and direct bilirubin, total protein, albumin, globulins, serum ferritin and calcium.

Discussion

Although Palestine is one of the Mediterranean basin countries in which thalassemias are prevalent, few studies had been carried out on the disease. Sirdah et al. [14] showed that the overall prevalence of β-thalassemia in the Gaza Strip was 4.3%. Occurrence of hereditary hemochromatosis among β-thalassemia intermediate and β-thalassemia minor subjects in the Gaza Strip was assessed [15]. In addition, immunological assessment of β-thalassemic major children [16] and mutation spectrum was also performed [13]. However, no previous study was focused on biochemical and hematological characteristics of β-thalassemic Palestinian children and their association to type of *HBB* mutation in the Gaza Strip. Therefore, this study is the first in this regard and can be useful in improving management protocols, blood transfusions, and iron chelation for thalassemia patients.

The β-thalassemic Palestinian children screened in the present work showed a significantly altered hemogram, especially in red blood cell mass (RBC count, Hct, and Hb) and related indices (MCV and MCH), concomitant with a significantly obvious microcytosis without hypochromia. Severe anemic presentations were seen in patients with decreased hemoglobin and HCT, i.e., 30 and 31.2%, as compared to controls. Significant thrombocytosis and leukocytosis were also reported among the patients. Our hematological findings in β-thalassemic patients are comparable to the general clinical presentations reported for thalassemic cases requiring blood transfusion [2]. El Yazji [16] showed analogous results concerning RBC mass and WBC count in β-thalassemic Palestinian patients; however he did not report a significant difference in platelets between patients and controls. Comparable results have also been reported in other settings in different countries. Rigano et al. 2001 showed significantly altered hemograms with severe anemia, thrombocytosis and leukocytosis in their β-thalassemic Sicilian patients [17]. The occurrence of thromboembolic events in a clinically relevant proportion of patients with β-thalassemia has been reported, and the existence of chronic hypercoagulable state in β-thalassemia in childhood may contribute to the cardiac and pulmonary anomalies and thrombotic events in later stages of life [18].

Biochemical tests in terms of liver and kidney function tests, bilirubin, and protein profile revealed significant abnormalities in patients as compared to controls, which agreed with results obtained elsewhere [19-23]. The iron overload observed in β-thalassemic children could potentially induce hepatic toxicity and, consequently, increased bilirubin level arising from decreased activity of cytochrome c oxidase disrupting mitochondrial respiration [21]. The observed increase of serum uric acid concentrations in the thalassemic patients can be explained by rapid erythrocyte turnover in combination with decreased reabsorption of filtered uric acid from possibly damaged renal tubules [20].

Iron overload is the most important complication of blood transfusion in β-thalassemia patients [4,24], but iron chelation therapy is still unsatisfactory in the Gaza Strip. Many patients are suffering from very severe iron overload and most of them (86.8%) are mainly chelated through subcutaneous pumps or intramuscular injection. Both therapeutic methods are not preferred by patients, who find it painful and uncomfortable. In addition, the pumps are not always available or need continuous maintenance and repair. These children and their parents are hoping to switch to oral chelation therapy, assuming it is more comfortable and painless [25,26].

Table 7: Hematological characteristics according to patients' genotype.

Genotype	WBC X 10^9/L	RBC X 10^{12}/L	Hb (g /dL)	HCT (%)	MCV (fl)	MCH (pg)	MCHC (g /dL)	PLT 10^9/L	RDW %
Homozygous IVS-I-1	8.7 ± 5.4	3.5 ± 0.6	8.7 ± 1.4	27.7 ± 4.7	80.1 ± 4.3	25.2 ± 1.3	31.5 ± 0.5	319.3 ± 120.4	16.2 ± 5.8
Homozygous IVS-I-110	11.2 ± 11.5	3.1 ± 0.3	7.8 ± 0.7	24.3 ± 1.9	78.5 ± 3.4	25.0 ± 1.2	31.9 ± 0.5	365.8 ± 113.9	14.7 ± 1.1
Homozygous CD39	8.6 ± 2.9	3.3 ± 0.4	8.1 ± 1.1	25.2 ± 3.5	77.3 ± 5.6	24.8 ± 1.5	32.1 ± 0.4	292.0 ± 103.9	22.9 ± 13.2
Homozygous IVS-I-6	8.4 ± 1.5	*4.0 ± 0.4	7.9 ± 0.5	24.3 ± 1.7	*62.0 ± 11.9	*20.1 ± 3.6	32.4 ± 0.3	*549.3 ± 202.3	27.5 ± 11.1
Homozygous CD37	15.2 ± 10.2	3.1 ± 0.3	8.0 ± 0.7	25.1 ± 2.3	81.4 ± 0.7	25.9 ± 0.3	31.8 ± 0.3	263.0 ± 67.6	15.1 ± 2.3
Double heterozygous	24.5 ± 25.6	3.2 ± 0.3	7.4 ± 0.8	23.6 ± 2.4	75.1 ± 6.2	23.7 ± 2.2	31.5 ± 0.6	*521.3 ± 205.6	26.3 ± 12.5

* Significantly different value as compared to the other genotypes
WBCs: White Blood Cells; **RBCs:** Red Blood Cells; **Hb:** Hemoglobin; **HCT:** Hematocrit; **MCV:** Mean Corpuscular Volume; **MCH:** Mean Corpuscular Hemoglobin **MCHC:** Mean Corpuscular Hemoglobin Concentration; **PLT:** Platelets Count

Table 8: Biochemical characteristics according to patients Genotype.

Genotype	ALT U/L	AST U/L	Urea mg/dL	Creatinine mg/dL	Uric acid mg/dL	Total Bilirubin mg/dL	Direct Bilirubin mg/dL	Total Protein g/dL	Albumin g/dL	Globulin g/dL	Ferritin ng/mL	Calcium mg/dL	Phosphorus mg/dL
Homozygous IVS-I-1	36.4 ± 27.8	47.0 ± 20.2	24.1 ± 7.2	0.45 ± 0.04	*3.4 ± 1.0	0.78 ± 0.13	0.30 ± 0.04	6.4 ± 0.6	4.2 ± 0.2	2.2 ± 0.4	3585.2 ± 1621.5	9.3 ± 0.5	4.9 ± 0.6
Homozygous IVS-I-110	*144.2 ± 74.4	*127.8 ± 51.5	27.2 ± 6.3	0.47 ± 0.07	4.4 ± 0.9	1.22 ± 0.59	0.38 ± 0.13	6.6 ± 0.8	4.3 ± 0.1	2.3 ± 0.7	3725.2 ± 848.8	9.8 ± 0.3	4.7 ± 0.3
Homozygous CD39	75.1 ± 55.3	79.4 ± 43.7	22.1 ± 4.05	0.45 ± 0.05	4.4 ± 1.1	1.57 ± 1.27	0.60 ± 0.52	6.5 ± 0.6	4.3 ± 0.1	2.2 ± 0.5	4216.7 ± 2673.6	9.4 ± 0.3	4.7 ± 0.4
Homozygous IVS-I-6	36.0 ± 38.2	50.7 ± 26.0	*31.3 ± 4.04	0.50 ± 0.04	3.9 ± 0.7	0.77 ± 0.06	0.37. ± 0.06	6.4 ± 0.5	4.3 ± 0.5	2.1 ± 0.3	3276.3 ± 1276.8	9.2 ± 0.1	4.5 ± 0.2
Homozygous CD37	38.3 ± 22.2	60.0 ± 36.4	18.7 ± 7.6	0.49 ± 0.09	4.9 ± 1.7	0.77 ± 0.12	0.30 ± 0.01	6.3 ± 0.8	4.2 ± 0.5	2.0 ± 0.5	2899.3 ± 823.2	8.8 ± 0.9	*5.7 ± 0.9
Double heterozygous	41.5 ± 34.0	50.6 ± 30.5	22.1 ± 4.8	0.43 ± 0.09	4.4 ± 0.7	0.99 ± 0.51	0.33 ± 0.07	6.6 ± 0.6	4.3 ± 0.2	2.4 ± 0.5	2901.3 ± 963.0	9.0 ± 0.5	4.6 ± 0.7

* Significantly different value as compared to the other genotypes
ALT: Alanine Aminotransferase; **AST:** Aspartate aminotransferase

The significant positive correlation between WBC and PLT counts in our thalassemic patients could increase the risk of arterial or venous thrombotic manifestations due the PLTs activation as they adhere to neutrophils and monocytes [27]. Moreover, the negative correlations of PLT with Hb and Hct in the present work alerting intense venous thrombotic manifestations in severely anemic patients. On the other hand, the positive correlation of iron overload reflected by serum ferritin with hepatocellular injury as reflected by serum levels of aminotransferases (ALT and AST) should be considered well during the management of the patients, particularly because this injury was found to be reversible in in adult patients with acquired anemias [28].

While, the positive correlation of serum ferritin and deterioration of kidney function tests (creatinine and uric acid) could be attributed to the iron chelation therapy required to treat iron overload in those transfusion dependent thalassemic patients [20].

Calcium-phosphorus balance, which may be due to the use of iron chelators, is one of the factors that contribute to development of osteoporosis in thalassemic patients [29]. Therefore, as our patients are exhibiting significantly reduced levels of calcium and phosphorus together with the reported correlation between calcium and hepatocellular injury, regular nutritional assessments should be done with specific attention, but not limited, to iron-containing foods, calcium, and phosphorus. Calcium rich foods or calcium supplements could be encouraged to reduce the risk of osteoporosis [30].

The association of patient genotype to hematological and biochemical characteristics revealed significantly different characteristics for patients with the IVS-I-6 and IVS-I-110 mutations, as compared to other genotypes, which could reflect the severity of the mutations. Hematological and biochemical studies by others of other populations with similar or different mutation patterns showed significant changes in these characteristics between different mutations. In a Brazilian population where IVS-I-110, IVS-I-6 and IVS-I-1 are predominant mutations [31,32], Bertuzzo et al. [33] showed that IVS-I-1 was the relatively severe mutation and IVS-I-6 was the mildest one, while IVS1-110 was intermediate in severity. In a Pakistani study, Khattak et al. [34] reported a frame shift mutation, FR 8-9, to have the lowest hematological RBC parameters.

An interesting finding of the present study is the percentage of homozygosity among the β-thalassemia patients. About 55% of the β-thalassemia patients were found to be homozygous for the same *HBB* mutation. Similarly high percentages of homozygous β-thalassemia patients were found in other populations in Arab and other developing countries [35-37]. Consanguinity is suggested to increase the selection of homozygous states in thalassemic disorders [38]. The high degree of homozygosity in our patients reflects a high degree of consanguinity among the Palestinian people in the Gaza Strip [39]. Since consanguineous individuals have a higher probability of carrying the same alleles than less closely or non-related individuals, births from consanguineous marriages are more frequently homozygous for various alleles than those from non-consanguineous marriages [40]. Although consanguineous marriage is the choice of more than 10% of the world population, an overall decline in its popularity has been reported, particularly in developed nations. The available literature indicates a reduction in homozygosity related to the shift from consanguinity to panmixia or non-consanguineous marriage, which is expected to significantly decrease the incidence of recessive single-gene disorders and positively impact the health of future generations [41]. Finally, few limitations need to be considered, first is the relatively small number of patients in some genotypes (Homozygous IVS-I-6 and Homozygous CD37), second is

the patients with unidentified mutation, and last is the heterogeneity of patents in terms of frequency of blood transfusion, iron chelation and splenectomy.

In conclusion, deteriorated hematological and biochemical profiles were seen in the β-thalassemic patients of Gaza Strip, with possible correlations to genotype; this requires a more appropriate management protocol for those patients, especially with the severe mutation. Moreover, awareness and counseling efforts about the potential health-related risks of consanguinity on the individuals and on the population should be improved to significantly decrease the incidence of homozygosity of recessive single-gene disorders and consequently enhancing the health of future generations and reducing the burden of these relatively preventable disorders.

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