Journal of
Otorhinolaryngology, Hearing and Balance Medicine

MDPI

Article

Towards Comprehensive Newborn Hearing and Genetic Screening in Russia: Perspectives of Implementation

Svetlana Chibisova [1,2], Tatiana Markova [1,2], Evgenia Tsigankova [1,2] and George Tavartkiladze [1,*]

[1] Audiology Department, Russian Medical Academy of Continuous Professional Education, Moscow 125040, Russia; chibisovass@zdrav.mos.ru (S.C.)
[2] The Sverzhevskiy Otorhinolaryngology Healthcare Research Institute, Moscow 117152, Russia
* Correspondence: gtavartkiladze@audiology.ru

Abstract: The universal newborn hearing screening (NHS) program was implemented in Russia in 2008 to replace the high-risk newborn hearing screening. More than 95% coverage and significant improvement in early detection and intervention is achieved. Meanwhile, it was shown that current OAE-based hearing screening missed 13% of newborns with genetically ascertained hereditary sensorineural hearing loss (SNHL). The aim of the study is to assess the results of genetic investigation and NHS in a large cohort of Russian children with bilateral SNHL and to study the feasibility of implementation of combined hearing and genetic screening in Russia. Genetic, audiological and NHS data of 1292 pediatric patients with bilateral SNHL born in 2008–2021 were analyzed. *GJB2* sequencing was performed for all subjects, 644 patients had pathological *GJB2* genotype, 406 of them were homozygous for c.35delG variant. The group of 155 *GJB2*-negative patients were searched for other SNHL genes, The pathological genotypes were identified at 87 patients. The most frequent genes were *STRC* (21.8%), *USH2A* (16.1%), *OTOF* (8%) and *SLC26A4* (6.9%). Children with confirmed genetic etiology passed NHS in 21% of cases. The perspectives of implementation of national comprehensive newborn hearing and genetic screening including whole exome sequencing technologies are discussed.

Keywords: hereditary hearing loss; newborn hearing screening; genetic screening; *GJB2*-hearing loss; *DFNB1*; *STRC*; *USH2A*; *OTOF*; *SLC26A* genes; massive parallel sequencing; whole exome sequencing

Citation: Chibisova, S.; Markova, T.; Tsigankova, E.; Tavartkiladze, G. Towards Comprehensive Newborn Hearing and Genetic Screening in Russia: Perspectives of Implementation. *J. Otorhinolaryngol. Hear. Balance Med.* **2024**, *5*, 6. https://doi.org/10.3390/ohbm5010006

Academic Editor: Yu Sun

Received: 8 April 2024
Revised: 8 May 2024
Accepted: 13 May 2024
Published: 15 May 2024

1. Introduction

Early hearing detection and intervention is crucial for normal speech and language development of babies with congenital hearing loss which is recognized as an important factor for their cognitive, educational, psychological, and social well-being [1,2]. The universal newborn hearing screening (NHS) was proved to be the most efficient way for timely detection of hearing-impaired babies [3,4]. NHS programs are conducted in many countries on the national, regional or community levels [5,6]. Different protocols are used based on otoacoustic emission (OAE) or automated auditory brainstem response (AABR) registration or both methods. Newborns failed the screening (positive result) must receive timely audiologic evaluation. Considering the wide range of public health systems, the most recent recommendations for hearing screening implementation were reviewed and systematized by World Health Organization in 2021 [7].

The universal NHS program was implemented in Russia in 2008 to replace the hearing screening of newborns and infants of the first year of life based on high-risk registry. The Russian NHS program aims to identify the cases of unilateral and bilateral hearing loss more than 25 dB. The program is based on transient OAE registration before discharge from maternal hospital on the 3–4th day of life with subsequent re-screening of referred cases in outpatient pediatric clinics. Final screen referrals must be performed with full audiological assessment in pediatric audiological centres. The evolution of early hearing detection and

intervention system of newborns and infants of the first year of life in Russia is described in our previous work [8].

The main target condition for NHS is bilateral sensorineural hearing loss (SNHL), it is the most common type of congenital and perinatal hearing impairment. Pathogenic genotype is approved to be the leading cause, and *GJB2* gene is the most frequent one [9]. In Russian population the frequency of *GJB2* etiology ranges from 46% in general SNHL cohort to 65% in the cohort of infants of the first year of life [10,11].

About 150 genes are known to be related to nonsyndromic SNHL (Hereditary Hearing Loss Homepage: https://hereditaryhearingloss.org (accessed on 31 January 2024)). New genetic technologies make possible to perform analysis of many genes—from massive parallel sequencing (MPS) till whole genome sequencing (WES) [12–14]. In the studies applied MPS technique in large cohorts, the diagnostic rate of non-*GJB2*-related hearing loss ranged 16–48% [15–19].

Meanwhile, it had been reported that some infants with ascertained genetic etiology of SNHL pass the NHS (that means false-negative result), thereby they didn't receive timely diagnostic evaluation and intervention [20]. Minami et al. reported the 8.9% of patients with hereditary SNHL who passed NHS [21]. It was estimated that Russian NHS program missed about 13% of newborns with *GJB2*-related SNHL [11].

To solve the issue of timely detection of NHS false negatives with hereditary SNHL, the concurrent hearing and genetic screening were proposed [9,20,22]. It was assumed that it can provide timely detection of 60% of infants with delayed-onset prelingual SNHL and etiologic diagnosis for 40% of those with congenital SNHL [9].

Most extensive experience of concurrent hearing and genetic screening was obtained by Chinese colleagues. Wang et al. reported the results of the concurrent hearing and genetic screening in the largest nationwide cohort (nearly 1.2 million newborns) [22]. Newborns (blood spot specimens) were screened for twenty common variants *GJB2*, *SLC26A4*, *MT-RNR1*(*12SrRNA*) and *GJB3* genes. Among positive genetic screening children with hearing loss the false-negative rate of hearing screening was 11% (12/107), so genetic screening detected 13% (12/95) more hearing-impaired infants than hearing screening alone. Moreover, the proposed model of genetic screening was helpful in detection of babies with risk of ototoxicity (0.23% of all cohort). The summary of Chinese studies and their own results are presented by Luo et al. [23].

The conception of comprehensive hearing and genetic screening for Russian healthcare system was first proposed in 2010 by Tavartkiladze et al. [24]. It was based on detection of 35delG as this pathogenic variant has the highest carrier rate (up to 6%) in Russian population [25]. In the case of 35delG in one allele full *GJB2* sequencing should be performed. Babies homozygous for 35delG must be referred to audiological assessment in both pass and refer hearing screening result. Taken into account the availability of new genetic technologies, this conception is to be reviewed.

The purpose of the study is to assess the results of NHS and genetic investigation in a large cohort of Russian children with bilateral SNHL and to study the feasibility of implementation of combined hearing and genetic hearing screening in Russia to improve early detection of congenital hereditary SNHL.

2. Materials and Methods

2.1. Study Population

The study sample includes 1292 children with bilateral SNHL who were born in 2008–2021 since the national universal NHS program was implemented. 690 of them are males (53.4%), 602—females (46.6%), that nearly corresponds to sex distribution for the age group 0–14 years (51.4% and 48.6%, respectively) reported by national statistical service (https://rosstat.gov.ru/storage/mediabank/bul_chislen_nasel-pv_01-01-2023.rar (accessed on 7 May 2024)).

The patients were recruited at the National Research Centre for Audiology and Hearing Rehabilitation (Moscow, Russia), the tertiary-level clinical facility of the Audiology

Department, Russian Medical Academy of Continuous Professional Education. The initial or confirmatory audiological evaluation was performed due to NHS fail result or parents/caregivers/medical specialists concern about child's hearing. Next step was genetic counseling when the patients were assessed as non-syndromal (i.e., the hearing deficit was the only symptom) and thereby were offered to participate in the study with referral for *GJB2* gene testing. In the study sample the median age of diagnosis was 6 months (interquartile range 2–16 months, range 1–65 months). The median age of genetic counseling and inclusion in the study was 18 months (interquartile range 8–33 months, range 1–105 months). The final stage of the study was the referral of *GJB2*-negative patients to the extended genetic MPS testing.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Russian Medical Academy of Continuous Professional Education (protocol #5 on 16 May 2017). Informed consent was obtained from all subjects involved in the study.

2.2. Audiological Evaluation

Hearing thresholds were obtained by age-appropriate method. Pure-tone audiometry (AC-40, Interacoustics AS, Middelfart, Denmark) was performed for children of 3 years and older (conditional audiometry mode for children 3–7 years old). For children less than 3 years old ABR were registered (Eclipse, Interacoustics AS, Middelfart, Denmark). Tympanometry (AZ-26, Interacoustics AS, Middelfart, Denmark) was done for all patients to avoid elevation of hearing thresholds due to transient conditions of the middle ear.

The severity of hearing loss was determined by average threshold at frequencies 500, 1000, 2000, 4000 Hz or an ABR wave V visual detection threshold on the better hearing ear. Hearing loss was classified as mild (26–40 dB HL), moderate (41–55 dB HL), moderately severe (56–70 dB HL), severe (71–90 dB HL), and profound (>90 dB HL).

2.3. Genetic Investigation

Molecular genetic investigation of the *GJB2* gene was performed to all patients. Most of them were tested in DNA Diagnostics laboratory at the Research Centre for Medical Genetics (Moscow, Russia) with DNA analysis previously described in [10]. The most frequent pathogenic variants in our cohort were c.35delG, c.-23+1G>A (1VSI+IG>A), c.101T>C (p.Met34Thr), c.167delT, c.235delC, c.313_326del14, c.358360delGAG (p.Glu120del), 101 kbdel (G.JB2-D135175) (NC 000013.10: g.20.757.021_20,858,394del) and 309kbdel(G.JB6-D13S1830) (NC 000013.10:g.20.797,17721,105.945).

Further genetic testing was mainly the MPS panel of 33 genes associated with SNHL (*STRC*, *MYO7A*, *MYO15A*, *TECTA*, *SLC26A4*, *CDH23*, *USH2A*, *TMPRSS3*, *TMC1*, *COL11A2*, *OTOF*, *EYA1*, *OTOA*, *PCDH15*, *ADGRV1*, *KCNQ4*, *LOXHD1*, *WFS1*, *MYH14*, *MYO6*, *ACTG1*, *PTPRQ*, *MYH9*, *OTOGL*, *TRIOBP*, *CLDN14*, *LRTOMT*, *PJVK*, *TPRN*, *WHRN*, *ALMS1*, *POU3F4*, *SMPX*), developed in DNA Diagnostics laboratory at the Research Centre for Medical Genetics (Moscow, Russia). The method was previously described in [19]. Several patients reported the results of WES analysis performed in private genetic laboratories; the data obtained were also included in the analysis.

All patients underwent medical genetic counseling before genetic testing and after receiving the results of genetic testing.

2.4. Newborn Hearing Screening

UNHS results were obtained from medical documentation for 540 participants. Other patients were not screened or had no documented NHS results. NHS was based on OAE registration and was performed in different maternal hospitals or outpatient clinics on different equipment allowed for clinical use by Federal Service for Surveillance in Healthcare, mostly OtoRead device (Interacoustics AS, Middelfart, Denmark). The "Refer" was marked if OAE was not registered in one or both ears and the test result was inconclusive. The "Pass" was marked if OAE was registered on both ears.

2.5. Statistical Analysis

Data collection and statistical analysis were carried out using the Snailbase Medical Data storage and analysis system (National Research Centre for Audiology and Hearing Rehabilitation, Moscow, Russia) and the Statistical Package R (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org (accessed 7 May 2024)). The differences in the frequencies of nominative variables were determined with the χ^2 test. The differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Genetic Investigation

In the study cohort of 1292 patients with bilateral SNHL pathologic genotype were found in 731 (57%) cases (gene-positive group). Most children underwent the first audiological investigation during first year of life. In 644 patients two pathogenic variants were detected in *GJB2* gene (*GJB2*-positive group) and 87 patients were identified with pathologic genotype in other genes (other genes-positive group). 68 patients, who were not identified with pathological genotype in other genes, and 493 patients with negative *GJB2* result (one or no pathogenic variants), for whom further genetic investigation was not performed, were combined in gene-negative group (Figure 1).

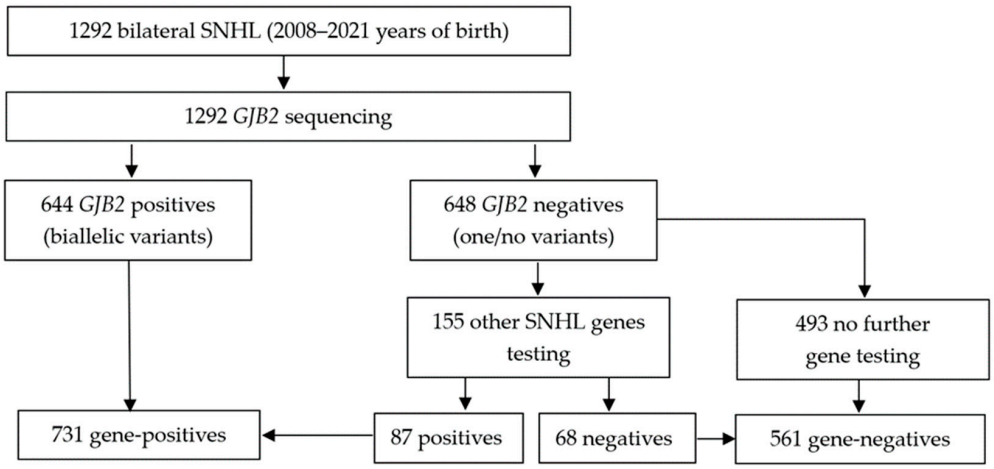

Figure 1. The results of genetic investigation in the study sample. SNHL—sensorineural hearing loss.

Among 644 *GJB2*-positives 569 patients had two truncating variants (T/T genotype). The one truncating and other non-truncating variant (T/NT genotype) were identified at 56 patients, 19—non-truncating variants in both alleles (NT/NT genotype). Among *GJB2* participants 406 were c.35delG homozygous, 181—c.35delG compound heterozygous. The allelic frequency of c.35delG variant in the *GJB2*-positive group is 77.1% (993/1288 chromosomes), that makes it the most frequent among identified pathogenic variants of *GJB2* gene and among identified truncating variants. Other frequent truncating variants are—c.23+1G>A—5.1% (66/1288), c.313_326del14—5% (64/1288), c.235delC—1.8% (23/1288) and c.167delT—1.4% (18/1288). Non-truncating variants are presented with p.Met34Thr—2.7% (35/1288), p.Val37Ile—1.2% (15/1288) and p.Leu90Pro—1% (13/1288). Total allelic frequency of these variants exceeds 95% (Table 1). Large deletion of *GJB6* gene was identified in our cohort as a common variant for the Ingush population.

Further genetic investigation of 155 *GJB2*-negative patients revealed 87 more subjects with ascertained hereditary etiology of SNHL (56%, 87/155) and 6.7% (87/1292) additional gene-positive cases were identified. The most affected gene is *STRC*—21.8% (19 patients) followed by *USH2A*—16.1% (14 patients), *OTOF*—8% (7 patients), *SLC26A4*—6.9% (6 patients), *ADGRV1*—5.7% (5 patients), *PAX3*—4.6% (4 patients), *MYO15A* 4.6% (4 patients), *CDH23*—3.4% (3 patients) and *MYO7A*—3.4% (3 patients). The diagnostic rate of these nine genes is 75%, the diagnostic rate of other 19 genes accounts for 25%. The effectiveness of

comprehensive genetic investigation in our study is 56%. If complete genetic testing were performed in 493 children, who were not received it, then 276 additional cases of genetic SNHL could be confirmed.

Table 1. Allelic frequencies of pathogenic variants in *GJB2*-positive group.

Genotype	Number of Alleles	% (n = 1288)
c.35delG	993	77.1
c.-23+1G>A	66	5.1
c.313_326del14	64	5.0
c.235delC	23	1.8
c.167delT	18	1.4
c.101T>C (p.Met34Thr)	35	2.7
c.109G>A (p.Val37Ile)	15	1.2
c.269T>C (p.Leu90Pro)	13	1.0
Total 8 most frequent variants	1227	95.3
Other 20 *GJB2* variants	61	4.7

3.2. Audiological Evaluation

The main audiological characteristic to be analyzed is the severity of hearing loss on the better hearing ear in patients depending on genetical findings (Table 2 and Figure 2). The whole study sample is distributed as 7% mild, 12% moderate, 15% moderately severe, 49% severe and 17% profound SNHL. The total rate of severe and profound cases accounts for 66% that is somewhat controversial to the epidemiological data on severity structure of hearing loss with most prevalent mild and moderate cases [2]. This fact can be explained by expert level of the clinical facility as one of the national cochlear implantation centers where the participants had been recruited, many of them were candidates for cochlear implantation due to significant hearing loss.

Table 2. Distribution of the study cohort by hearing loss severity and genotype.

Genotype	Severity					
	Mild	Moderate	Moderately Severe	Severe	Profound	Total
GJB2-positives	30	62	86	344	122	644
%	5	10	13	53	19	100
T/T	6	47	70	331	115	569
%	1	9	12	58	20	100
[35delG]×2	6	31	50	231	88	406
%	1	8	12	57	22	100
other T/T	0	16	20	100	27	163
%	0	10	12	61	17	100
T/NT	14	11	14	11	6	56
%	25	20	25	20	10	100
NT/NT	10	4	2	2	1	19
%	52	21	11	11	5	100
Other genes-positives	14	20	26	25	2	87
%	16	23	30	29	2	100
Gene-negatives	47	78	77	264	95	561
%	8	14	14	47	17	100
Total cohort	91	160	189	633	219	1292
%	7	12	15	49	17	100

T/T—truncating variants in both alleles, T/NT—one truncating and one non-truncating variants, NT/NT—non-truncating variants in both alleles.

(**a**) (**b**)

Figure 2. Distribution of patients by hearing loss severity and genotype. (**a**) comparison between *GJB2*-positive group, other genes-positive group and gene-negative group; (**b**) comparison between different *GJB2* genotypes groups—c.35delG homozygotes (c.35delGx2), other T/T genotypes, T/NT and NT/NT genotypes. T—truncating variant, NT—non-truncating variant.

The distribution in *GJB2*-positive group tends to be more severe than in gene-negative group—53% severe and 19% profound *GJB2*-related cases vs. 47% and 17% gene-negative cases, respectively ($p = 0.007$). The more significant difference is found in paired comparison of other genes-positive group with *GJB2*-positive group and gene-negative group ($p < 0.001$ for both). The significant difference is also observed between T/T, T/NT and NT/NT subgroups ($p < 0.01$). More precise analysis in the T/T group shows that the difference between 35delG homozygotes and other T/T genotypes is not significant ($p = 0.290$). Interestingly, all six patients with mild SNHL and T/T genotype were 35delG homozygotes.

3.3. Results of Newborn Hearing Screening

The results of NHS were verified in 540 patients, and they were included in the analysis. Other patients were not screened or had no NHS documentation. The total pass rate is 19.3% (104/540), in gene-positive group—21% (71/340) and in gene-negative group—17% (33/200) (Table 3). The difference of pass rate in gene-positive and gene-negative SNHL patients is not significant ($p = 0.213$).

Table 3. NHS results in gene-positive and gene-negative groups.

NHS Result	Gene-Positives	Gene-Negatives	Total
Refer	269	167	436
Pass	71	33	104
Total	340	200	540

Among gene-positive patients with verified pass NHS result five were identified with *OTOF* pathological genotype and audiological features of auditory neuropathy spectrum disorder. Given the fact of OAE-based protocol, these patients could not be identified by NHS and corrected pass rate can be estimate as 19.7% (66/335).

4. Discussion

The universal NHS program was implemented in Russia in 2008 to improve early detection and intervention of babies with congenital SNHL. Ministry of Healthcare and regional audiological centres report more than 95% coverage of newborns in maternal facilities and outpatient clinics [8]. Besides NHS, the innovative genetic technologies became available in the federal research centres and private genetic laboratories to elucidate the hereditary etiology of congenital hearing impairment. Meanwhile, cases of infants with confirmed hereditary hearing loss who passed the NHS were reported [11]. The precise

analysis needs to be done to provide quality control and continuous improvement of the national NHS program. In our opinion, the genetic test for *GJB2* gene can serve as a quality indicator of NHS program.

The aim of the study was to assess the results of genetic investigation and NHS in a large cohort of 1292 children with bilateral SNHL born since the implementation of national NHS program. Genetic etiology was confirmed in 57% of the study sample including 50% with pathological genotype in *GJB2* gene and 7% in other SNHL-related genes. The most frequent pathogenic variant in the current is 35delG with 77% allelic frequency that is explained by its' high carrier rate in Russian population [25]. Totally eight most frequent pathogenic variants account for 95% of all found variants. The studies on genetic landscape of SNHL found different mutation frequencies depending on ethnic specificity of population but *GJB2* gene is always the leading cause [9,15–17].

The correlation of *GJB2* truncating and non-truncating pathogenic variants with severity of hearing loss found in this study corresponds with other large cohort studies [21,26]. The T/T genotype shows significantly more severe and profound hearing loss than T/NT and NT/NT genotypes ($p < 0.01$) while no significant difference was found between 35delG homozygotes and other T/T genotypes ($p = 0.290$). Surprisingly, all six patients with mild SNHL and T/T genotype were 35delG homozygotes that supports the known phenomenon of high clinical heterogeneity of *GJB2*-related SNHL.

The comprehensive genetical testing in 155 patients was 56% effective in confirmation of other than *GJB2* affected genes as causative for SNHL. *STRC*, *USH2A*, *OTOF*, *SLC26A*, *ADGRV1*, *PAX3*, *MYO15A*, *CDH23* and *MYO7A* account for 75% of all positive results. The similar genes were revealed as most frequent in other studies [15–19].

Initially all cases of SNHL included in the study were defined as non-syndromal due to the fact that hearing impairment was the only known clinical deficit at the time of recruitment in the study. As the result of extended genetic investigation of 33 genes, including some genes of syndromal SNHL, substantial part of the SNHL cases in our study sample were ascertained as true non-syndromal. Several patients with primary hearing deficit and suspected manifestation of syndromes associated with hearing loss like Usher or Pendred were identified and referred to appropriate clinical assessment.

Another main finding of the current study is that the pass rate is quite similar in gen-positive and gen-negative SNHL patients—21% and 17%, respectively ($p = 0.213$). Thereby, it can be supposed that the high pass rate in these patients depends on program performing defects. This finding is controversial to the hypothesis of non-penetrance at birth and true delayed onset hearing loss in some *GJB2*-positive patients [20].

The study shows a lack of medical documentation of NHS results and low parental awareness as we failed to obtain verified results in 58% of participants. Till now there is no unified system on reporting NHS results in the whole country though the State medical information system has been implemented since 2016. Thereby there is a need to incorporate NHS reporting in the national medical database.

Given the high pass rate in hereditary SNHL patients and the leading role of genetics in SNHL etiology, the Russian perspectives of introducing the comprehensive hearing and genetic screening must be discussed in multidisciplinary team of audiologists, geneticists and public health professionals.

Since 2023, the program of extended neonatal screening for 36 rare disorders has been running [27]. The neonatal screening register has been developed and incorporated within specialized medical information system AkiNeo to track the results (https://vimis.ncagp.ru (accessed on 7 May 2024)). For each newborn the test-blank with blood samples is labeled with unique test-code based on the date of blood draw and the number of medical birth certificate. The same blood samples can be used for genetic screening for most frequent *GJB2* pathogenic variants and other SNHL-related genes to solve the problem of late identification of newborns with congenital hereditary SNHL who are missed by NHS. The results of the current study and other studies in Russian cohorts [19,22] provide evidence for the design of the most appropriate test kit for Russian population. It must definitely

include the truncating *GJB2* variants c.35delG, c.-23+1G>A and c.313_326del14 as they usually lead to severe and profound hearing loss and totally account for almost 90% of allele frequency. The *OTOF* gene is the first candidate to be screened among non-*GJB2* genes as one of the main causes of auditory neuropathy spectrum disorders. Such cases are missed by the current OAE-based NHS protocol and cochlear implantation is the only effective method that provides excellent rehabilitation outcomes.

Recently the first national newborn genetic screening on the basis on whole genome sequencing (WES-screening) project "EXAMEN" has been started in the Kulakov National Medical Research Centre for Obstetrics, Gynecology and Perinatology (https://clinicaltrials.gov/study/NCT05325749 (accessed on 7 May 2024)) [28]. It is aimed to obtain the initial experience of the inclusive genetic screening of newborn in Russia, to develop the methodology of creation of the newborn genetic health record and to assess frequencies of mid and low penetrance hereditary disorders in Russian population. The residual cord blood is collected to perform WES in two modes. First is the basic screening of newborns without developmental features having no variations according to a conventional newborn screening for inherited diseases. Families are provided with a report about pathogenic or likely pathogenic variants identified in genes associated with childhood-onset diseases for which specific care or prevention protocols are available. Second is extended screening of newborns showing either phenotypic features or deviations according to mass spectrometry screening. Families who signed additional informed consent will receive an advanced report including variants with no care or prevention available, mid or low risk variants, and variants with late onset or those suggesting relatives to undergo screening. Detailed information can be seen on the project site https://exome.ncagp.ru/specialists.php (accessed on 8 May 2024). The similar WES projects named BabySeq and Baby Beyond Hearing has been reported recently [29,30]. The possible role of WES-screening for early detection of multiple diseases including congenital SNHL in Russia is currently discussed [28,31].

Besides the evident benefits, the ethical considerations for WES are actively discussed meaning possible psychological harm on subjects identified with pathogenic variants and unknown probability of penetrance or time of manifestation of the disease [32]. Meanwhile, hereditary SNHL is a high-prevalent health condition with well-recognized natural history and effective rehabilitative strategies to provide full social integration to affected children. Incorporation of WES within early hearing detection and intervention system can provide immediate etiological diagnosis to perform highly personalized rehabilitation strategy.

5. Conclusions

The study has shown the 57% of genetic etiology in Russian large cohort of children with congenital bilateral SNHL predominantly caused by *GJB2*, *STRC*, *USH2A*, *SLC26A4* and *OTOF* pathogenic variants. Meanwhile, 21% of children with genetically confirmed SNHL were missed by national NHS program that is not significantly different from false-negative rate in children unidentified with genetic etiology. This finding must be concerned with performing defects of the NHS program. All findings point out the necessity of implementing the comprehensive hearing and genetic screening based on innovative genetic technologies which are already available in Russia.

Author Contributions: Conceptualization, T.M., S.C. and G.T.; methodology, T.M. and S.C.; software S.C.; validation, T.M. and S.C.; formal analysis, T.M. and S.C.; investigation, T.M. and S.C.; resources, T.M. and S.C.; data curation, S.C.; writing—original draft preparation, T.M. and S.C.; writing—review and editing, E.T. and G.T.; visualization, S.C.; supervision, E.T. and G.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Russian Medical Academy of Continuous Professional Training (protocol #5 on 16 May 2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Dataset available on request from the authors.

Acknowledgments: The authors want to acknowledge specialists of the DNA Diagnostics laboratory at the Research Centre for Medical Genetics (Moscow, Russia) for the long-term collaboration in the field of hereditary hearing loss research in Russia.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Fitzpatrick, E. Neurocognitive development in congenitally deaf children. *Handb. Clin. Neurol.* **2015**, *129*, 335–356. [CrossRef] [PubMed]
2. World Health Organization. *World Report on Hearing*; World Health Organization: Geneva, Switzerland, 2021.
3. Joint Committee on Infant Hearing. Year 2019 position statement: Principles and guidelines for early hearing detection and intervention programs. *J. Early Hear. Detect. Interv.* **2019**, *4*, 1–44. [CrossRef]
4. Ching, T.Y.C.; Leigh, G. Considering the impact of universal newborn hearing screening and early intervention on language outcomes for children with congenital hearing loss. *Hear. Balance Commun.* **2020**, *18*, 215–224. [CrossRef] [PubMed]
5. Neumann, K.; Mathmann, P.; Chadha, S.; Euler, H.A.; White, K.R. Newborn hearing screening benefits children, but global disparities persist. *J. Clin. Med.* **2022**, *11*, 271. [CrossRef] [PubMed]
6. Bussé, A.M.L.; Mackey, A.R.; Hoeve, H.L.J.; Goedegebure, A.; Carr, G.; Uhlén, I.M.; Simonsz, H.J.; EUS€REEN Foundation. Assessment of hearing screening programmes across 47 countries or regions I: Provision of newborn hearing screening. *Int. J. Audiol.* **2021**, *60*, 821–830. [CrossRef] [PubMed]
7. World Health Organization. *Hearing Screening: Considerations for Implementation*; World Health Organization: Geneva, Switzerland, 2021. Available online: https://www.who.int/publications/i/item/9789240032767 (accessed on 7 May 2024).
8. Tavartkiladze, G.A.; Chibisova, S.S.; Markova, T.G.; Yasinskaya, A.A.; Tufatulin, G.S.; Volodin, N.N. Formation, development and enhancement of the system of audiological screening of newborns and children of the first year of life in Russia. *J. Pediatr. Named After G.N. Speransky* **2023**, *102*, 18–26. (In Russian) [CrossRef]
9. Morton, C.C.; Nance, W.E. Newborn hearing screening—A silent revolution. *N. Engl. J. Med.* **2006**, *354*, 2151–2164. [CrossRef]
10. Bliznetz, E.A.; Galkina, V.A.; Matyushchenko, G.N.; Kisina, A.G.; Markova, T.G.; Polyakov, A.V. Changes in the connexin 26 gene (*GJB2*) in Russian patients with hearing loss: Results of long-term molecular diagnostics of hereditary nonsyndromic hearing loss. *Russ. J. Genet.* **2012**, *48*, 101–112. [CrossRef]
11. Lalayants, M.R.; Markova, T.G.; Bakhshinyan, V.V.; Bliznetz, E.A.; Polyakov, A.V.; Tavartkiladze, G.A. The audiological phenotype and the prevalence of *GJB2*-related sensorineural loss of hearing in the infants suffering acoustic disturbances. *Vestn Otorinolaringol* **2014**, *79*, 37–43. (In Russian)
12. Abou Tayoun, A.N.; Al Turki, S.H.; Oza, A.M.; Bowser, M.J.; Hernandez, A.L.; Funke, B.H.; Rehm, H.L.; Amr, S.S. Improving hearing loss gene testing: A systematic review of gene evidence toward more efficient next-generation sequencing-based diagnostic testing and interpretation. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **2016**, *18*, 545–553. [CrossRef]
13. Bademci, G.; Foster, J., 2nd; Mahdieh, N.; Bonyadi, M.; Duman, D.; Cengiz, F.B.; Menendez, I.; Diaz-Horta, O.; Shirkavand, A.; Zeinali, S.; et al. Comprehensive analysis via exome sequencing uncovers genetic etiology in autosomal recessive nonsyndromic deafness in a large multiethnic cohort. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **2016**, *18*, 364–371. [CrossRef] [PubMed]
14. Mitchell, C.O.; Morton, C.C. Genetics of childhood hearing loss. *Otolaryngol. Clin. N. Am.* **2021**, *54*, 1081–1092. [CrossRef]
15. Sloan-Heggen, C.M.; Bierer, A.O.; Shearer, A.E.; Kolbe, D.L.; Nishimura, C.J.; Frees, K.L.; Ephraim, S.S.; Shibata, S.B.; Booth, K.T.; Campbell, C.A.; et al. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. *Hum. Genet.* **2016**, *135*, 441–450. [CrossRef]
16. Baux, D.; Vache, C.; Blanchet, C.; Willems, M.; Baudoin, C.; Moclyn, M.; Faugere, V.; Touraine, R.; Isidor, B.; Dupin-Deguine, D.; et al. Combined genetic approaches yield a 48% diagnostic rate in a large cohort of French hearing-impaired patients. *Sci. Rep.* **2017**, *7*, 16783. [CrossRef] [PubMed]
17. Del Castillo, I.; Morín, M.; Domínguez-Ruiz, M.; Moreno-Pelayo, M.A. Genetic etiology of non-syndromic hearing loss in Europe. *Hum. Genet.* **2022**, *141*, 683–696. [CrossRef] [PubMed]
18. Shearer, A.E.; Shen, J.; Amr, S.; Morton, C.C.; Smith, R.J.; Newborn Hearing Screening Working Group of the National Coordinating Center for the Regional Genetics Networks. A proposal for comprehensive newborn hearing screening to improve identification of deaf and hard-of-hearing children. *Genet. Med.* **2019**, *21*, 2614–2630. [CrossRef] [PubMed]
19. Shatokhina, O.; Galeeva, N.; Stepanova, A.; Markova, T.; Lalayants, M.; Alekseeva, N.; Tavarkiladze, G.; Markova, T.; Bessonova, L.; Petukhova, M.; et al. Spectrum of genes for non-*GJB2*-related non-syndromic hearing loss in the Russian population revealed by a targeted deafness gene panel. *Int. J. Mol. Sci.* **2022**, *23*, 15748. [CrossRef] [PubMed]
20. Norris, V.W.; Arnos, K.S.; Hanks, W.D.; Xia, X.; Nance, W.E.; Pandya, A. Does universal newborn hearing screening identify all children with *GJB2* (Connexin 26) deafness? Penetrance of GJB2 deafness. *Ear Hear.* **2006**, *27*, 732–741. [CrossRef] [PubMed]
21. Minami, S.B.; Mutai, H.; Nakano, A.; Arimoto, Y.; Taiji, H.; Morimoto, N.; Sakata, H.; Adachi, N.; Masuda, S.; Sakamoto, H.; et al. *GJB2*-associated hearing loss undetected by hearing screening of newborns. *Gene* **2013**, *532*, 41–45. [CrossRef]
22. Wang, Q.; Xiang, J.; Sun, J.; Yang, Y.; Guan, J.; Wang, D.; Song, C.; Guo, L.; Wang, H.; Chen, Y.; et al. Nationwide population genetic screening improves outcomes of newborn screening for hearing loss in China. *Genet. Med.* **2019**, *21*, 2231–2238. [CrossRef]

23. Luo, H.; Yang, Y.; Wang, X.; Xu, F.; Huang, C.; Liu, D.; Zhang, L.; Huang, T.; Ma, P.; Lu, Q.; et al. Concurrent newborn hearing and genetic screening of common hearing loss variants with bloodspot-based targeted next generation sequencing in Jiangxi province. *Front. Pediatr.* **2022**, *10*, 1020519. [CrossRef] [PubMed]
24. Tavartkiladze, G.A.; Poliakov, A.V.; Markova, T.G.; Lalaiants, M.R.; Bliznets, E.A. Genetic screening for hearing disorders in newborn infants in combination with audiological screening. *Vestn. Otorinolaringol.* **2010**, *75*, 15–18. (In Russian)
25. Posukh, O.L. Genetic etiology of hearing loss in Russia. *Hum. Genet.* **2022**, *141*, 649–663. [CrossRef] [PubMed]
26. Snoeckx, R.L.; Huygen, P.L.; Feldmann, D.; Marlin, S.; Denoyelle, F.; Waligora, J.; Mueller-Malesinska, M.; Pollak, A.; Ploski, R.; Murgia, A.; et al. GJB2 mutations and degree of hearing loss: A multicenter study. *Am. J. Hum. Genet.* **2005**, *77*, 945–957. [CrossRef] [PubMed]
27. Voronin, S.V.; Kutsev, S.I. Neonatal screening for hereditary diseases in Russia: Yesterday, today, and tomorrow. *Neonatol. News Opin. Train.* **2022**, *10*, 34–39. (In Russian) [CrossRef]
28. Shubina, Y.; Pavlova, N.; Donikov, A.; Pomeranzeva, Y.A.; Trofimov, D. Perspectives and limitations of whole exome based neonatal screening. *Neonatol. News Opin. Train.* **2022**, *10*, 40–46. (In Russian) [CrossRef]
29. Holm, I.A.; Agrawal, P.B.; Ceyhan-Birsoy, O.; Christensen, K.D.; Fayer, S.; Frankel, L.A.; Genetti, C.A.; Krier, J.B.; LaMay, R.C.; Levy, H.L.; et al. The BabySeq project: Implementing genomic sequencing in newborns. *BMC Pediatr.* **2018**, *18*, 225. [CrossRef] [PubMed]
30. Downie, L.; Halliday, J.; Lewis, S.; Lunke, S.; Lynch, E.; Martyn, M.; Gaff, C.; Jarmolowicz, A.; Amor, D.J. Exome sequencing in newborns with congenital deafness as a model for genomic newborn screening: The Baby Beyond Hearing project. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **2020**, *22*, 937–944. [CrossRef]
31. Baranova, E.E.; Zobkova, G.Y.; Vorontsova, M.V.; Izhevskaya, V.L. Ethical issues of genome screening: Review. *Med. Genet.* **2021**, *20*, 3–14. (In Russian) [CrossRef]
32. Mitchell, C.O.; Rivera-Cruz, G.; Chau, M.H.K.; Dong, Z.; Choy, K.W.; Shen, J.; Amr, S.; Giersch, A.B.S.; Morton, C.C. The burden and benefits of knowledge: Ethical considerations surrounding population-based newborn genome screening for hearing. *Int. J. Neonatal Screen.* **2022**, *8*, 36. [CrossRef]