Natural history questionnaire for families/legal representatives of the individuals affected by DHX30-related neurodevelopmental disorders.

Dear parents and legal representatives of the individuals affected by DHX30-related syndromes,

We are contacting you because we need YOUR help to understand this rare genetic syndrome.

For every rare disease, it's critical to gain deep knowledge on the clinical signs and symptoms, progression, and therapeutic options that may have ameliorated some symptoms in your children. Only by conducting such studies we will be able to let you and new families know what to expect in the future regarding the progression in your children. Moreover, this is a precondition for developing an effective clinical trial. That's why we are starting this "family-based natural history study". A natural history study is a medical research study that focuses on the disease progression and patient population.

Therefore, we would like to ask you to take your time and try to give us as much information as possible. Should you have any doubts or questions do not hesitate to contact us.

With best regards,

Prof. Davor Lessel, MD, PhD

Dr. Olena Ielesicheva

1. Background Information:			
Your name:		Relationship to the patient:	
Contact phone:		Contact email:	
Patient' s name:			
Patient' s gender:			
Patient' s ethnicity:			
Country:			
Current age:			
Current weight:			Kg
Current length:			Cm
Age of diagnosis of DHX30-related syndrome in months (years):		Years Months	
Date of this genetic testing:			
Result of this genetic testing:			
DHX30 variant as in genetic report:			

2. Family history *(Please choose **yes** or **no**)*				
Do you or your partner (mother/father of the patient) have any hereditary diseases in your family?	Yes		No	
If yes, then specifically which ones?				
Are you and your partner blood relatives?	Yes		No	

3. Problems in previous pregnancies *(Please, answer the next questions)*	
How many pregnancies did you have?	
How many deliveries?	
What kind of deliveries (natural, Caesarean section…)?	

Did you have pregnancy loss/miscarriage?		Yes		No	
	If so, how many times?				
Did you have previous preterm labor?		Yes		No	
	If so, how many times?				
Any birth defects or genetic conditions in previous children/ fetuses?		Yes		No	
	If so, what kind?				
Did you have infertility in history?		Yes		No	
	If so, what was the cause?				
How many years of infertility did you have?					
Please provide any additional information regarding previous pregnancies that you may additionally find important:					

4. Chronic Diseases *(Please, answer the next questions)*				
Do you or your partner (mother/father of the patient) suffer from any chronic diseases?	Yes		No	
If so, what kind?				
Do you or your partner (mother/father of the patient suffer from any chronic infections? (hepatitis B, C, HIV/AIDC) hepatitis B, C	Yes		No	
Please provide any additional information regarding another disorders, that you may additionally find important.				

5. Environmental Factor *(Please, answer the next questions)*	
Where did you or your partner (mother/father of the patient) work before and during pregnancy?	

6. Harmful habits *(Please, answer the next questions)*				
Do you or your partner (mother/father of the patient) have harmful habits?	Yes		No	
Alcohol use	Yes		No	

Tobacco use	Yes		No	
Drug use	Yes		No	
Other harmful habits not listed above:				

7. Problems during the pregnancy *(Please, answer the next questions)*				
How old were you and your partner at the time of conception?	Mother:		Father:	
What kind of conception? (please choose the right one)	Spontaneous:		IVF:	
What was the screening test of the first trimester of pregnancy with the calculation of individual risk (if you remember)?				
What were the levels of biochemical markers during the screening test of the first trimester of pregnancy:	PAPP-A		MoM	
	b-hCG		MoM	

Was the nuchal translucency increased during the ultrasounds scan at 11-14 weeks of pregnancy?		Yes	Mm	No	
Did you have the complications during pregnancy?		Yes		No	
If so, which ones (please choose the appropriate option):					
	Severe nausea and vomiting in pregnancy	Yes		No	
	Iron deficiency anemia	Yes		No	
	High blood pressure	Yes		No	
	Gestational diabetes	Yes		No	
	Preeclampsia	Yes		No	
	Epilepsy	Yes		No	
	Hemorrhage (bleeding)	Yes		No	
	Unhealthy factors during pregnancy (infections, medications, X-ray, stress)	Yes		No	
Did you have prenatal fetal complications?		Yes		No	
If so, which ones (please choose the appropriate option):					
	Ultrasounds markers and abnormalities:	Yes		No	
	If so, what kind?				

	Did you conduct the amniocentesis						Yes		No	
	Placental Problems:						Yes		No	
	If so, what kind?									
	Level of amniotic fluid:	Normal		Increased		Decreased				
	Poor fetal growth:						Yes		No	
Please provide any additional information regarding other complications that you may additionally find important.										

8. Neonatal period (first 4 weeks of life) *(Please, answer the next questions)*										
1.	Type of delivery:									
	Normal spontaneous vaginal delivery						Yes		No	
	- Vacuum-assisted vaginal delivery	Yes		No		What was the reason?				
	- Cesarean section	Yes		No		What was the reason?				
	- Preterm delivery	Yes		No		What week?				
	- Delivery complications?	Yes		No		What kind?				
	- Birth trauma	Yes		No		What kind?				
2.	Birth at which week of gestation?									
3.	APGAR score:	1 min				5 min				
4.	Body values:									
	- Weight									g
	- Length									Cm
	- Head circumference									Cm
5.	Neonatal Complications						Yes		No	
If so, which ones (please choose the appropriate option):										
	Neonatal jaundice:						Yes		No	
	When started?	hours/days after the birth blood test				Level of bilirubin:				
	- Difficulty breathing at birth that gets progressively worse						Yes		No	
	- Blue color at birth						Yes		No	

	- Absent breathing for 20 seconds or longer	Yes		No	
	- Requiring the use of a mechanical ventilator and extra oxygen	Yes		No	
	- Using artificial surfactant	Yes		No	
	- Neonatal resuscitation	Yes		No	
	- Intraventricular hemorrhage	Yes		No	
	- Feeding difficulties	Yes		No	
	- Gastroesophageal reflux	Yes		No	
	- Rh incompatibility	Yes		No	
	- ABO-incompatibility	Yes		No	
	Please provide any additional information regarding another neonatal complications, that you know may additionally find important.				
6.	Presence of neonatal congenital anomalies	Yes		No	
7.	If so, please write about it, if you know:				
8.	Neurological signs (please choose yes or no):	Yes		No	
	If so, which ones (please choose the appropriate option):				
	- Neonatal seizures – seizures that take place during the first month of life	Yes		No	
	- Abnormally low muscle tone	Yes		No	
	- Floppy baby	Yes		No	
	- Changes in muscle tone (either high or low)	Yes		No	
	- Changes in body temperature	Yes		No	
	- Rapid changes in head size and tense soft spot	Yes		No	
	- Difficulty feeding and swallowing (refusal to eat and vomiting)	Yes		No	
	- Requiring tube feeding	Yes		No	
9.	Neonatal behavioral states: *(Please choose the correct option for your opinion)*				
	- Light sleep	Yes		No	
	- Minimal activity	Yes		No	
	- Active	Yes		No	
	- Crying with increased motor activity	Yes		No	

	Please provide any additional information regarding other signs that you know may additionally find important.	

9. Post-birth period (after 1 month from birth) *(Please, answer the next questions)*				
1.	**Age of skill development:**			
	- Age of holding own head up	Months	Not attained:	
	- Age of rolling over	Months	Not attained:	
	- Age of sitting	Months	Not attained:	
	- Age of crawling	Months	Not attained:	
	- Age of learning to walk	Months	Not attained:	
	- Age of walking without support	Months	Not attained:	
	- Age of first words	Months	Not attained:	
	- Age of learning to self-feed	Months	Not attained:	
	- Age of learning dressing	Months	Not attained:	
	- Age of learning potty training	Months	Not attained:	

2.	**Neurological signs:**				
	Does your child experience regression or lag in his/her development or social interactions?	Yes		No	
If your child has any of the following neurological symptoms, please choose the various signs, including past and present:					
Abnormal Movement:					
	- involuntary, rapid and repetitive stereotyped movements and sounds (including vocal tics)	Yes		No	
	- involuntary, repetitive shaking movement of the body	Yes		No	
	- muscle spasms or develop paralysis in certain parts of the body	Yes		No	
	- body muscles to twist into abnormal postures	Yes		No	
	- restless legs syndrome – a strong urge to move the legs, often during the onset of sleep	Yes		No	
Abnormal muscle tone:					
	- muscular weakness	Yes		No	
	- baby is not able to sit or hold up his head	Yes		No	
	- body parts are floppy or too stiff	Yes		No	

Motor development delay:					
	- delay crawling, sitting or walking	Yes		No	
	- unsteady posture, impaired coordination, often with poor balance and falling	Yes		No	
	- may seem clumsy or have trouble walking up and down stairs	Yes		No	
	- the child demonstrates fatigue and difficulty walking	Yes		No	
	- has difficulty holding small objects, such as toys, or performing activities such as tying shoelaces or brushing teeth	Yes		No	
	- needs wheelchair assistance	Yes		No	
Autism spectrum disorder:					
	- difficulties with social interaction, expressing or showing fear when interacting with new people	Yes		No	
	- does not make eye contact (does not look into the eyes)	Yes		No	
	- hyperactivity syndrome	Yes		No	
	- limited interests	Yes		No	
	- anxiety (social anxiety disorder)	Yes		No	
	- depression	Yes		No	
	- impulsive behavior	Yes		No	
	- outbursts of anger	Yes		No	
Impaired speech development and receptive language:					
	- speech delay or difficulty speaking	Yes		No	
	- difficulty understanding words or concepts	Yes		No	
	- trouble identifying colors, body parts or shapes	Yes		No	
	- reduced vocabulary of words and complex sentences for age	Yes		No	
	- slowly babbles, talks and makes sentences	Yes		No	
	- problems with oral motor skills, weakness of the muscles of the mouth or difficulty moving the tongue or jaw	Yes		No	
	- using words and gestures to communicate	Yes		No	
Intellectual disability:					
	- IQ-test				
	- learning difficulties	Yes		No	
	- communication difficulties	Yes		No	
	- difficulty remembering things	Yes		No	
	- attention deficit	Yes		No	
	- lack of curiosity	Yes		No	

	- problems with logical thinking	Yes		No	
	- trouble understanding rules and consequences	Yes		No	
	- slow to learn things like feeding, dressing or potty training	Yes		No	
Abnormal behavior					
	- infantile behavior that continues into preschool or school age	Yes		No	
	- self-harm, which includes hitting your head or body against other body parts or objects, biting yourself, scratching yourself, pinching yourself, and pulling your hair	Yes		No	
	- stereotyped, repetitive behavior	Yes		No	
	- aggressive acts or deliberate open attacks directed at other persons or objects	Yes		No	
Seizures					
	Has your child ever had seizures?	Yes		No	
Please check the different types of seizures that your child has, including past and present seizure types.					
a)	Type of seizures				
	- whole body shaking (grand mal, generalized, or secondary tonic-clonic)	Don't know		Yes		No	
	- stiffening of the whole body or part of the body (tonic seizures)	Don't know		Yes		No	
	- shaking of only part of the body (partial or focal motor seizures)	Don't know		Yes		No	
	- infantile spasms	Don't know		Yes		No	
	- staring spells (petit mal, absence or complex partial seizures)	Don't know		Yes		No	
	- very quick jerks or shaking (myoclonic)	Don't know		Yes		No	
	- drop spells (atonic seizures)	Don't know		Yes		No	
	- other (please specify)						
b)	Age of beginning (in years and months)	Years:		Months:			
c)	Frequency of these seizures						
	Single/Occasional		Per day		Per week		Per Month
d)	Time of day when seizures occur. (check all that apply):						
	Daytime		Evening		Sleeping		
e)	Any contributing factors? (check all that apply):						
	Fever		Infections		Lack of sleep		Other

f)	Has your child ever had seizures lasting longer than 15 minutes (status epilepticus)?	Don't know		Yes		No		
	If yes, how often does this situation occur?							
g)	Which medications do you use?	Have tried?				Currently on?		
	- Carbamazepine	Yes		No		Yes		No
	- Clobazam	Yes		No		Yes		No
	- Ethosuximide	Yes		No		Yes		No
	- Felbamate	Yes		No		Yes		No
	- Gabapentin	Yes		No		Yes		No
	- Lamotrigine	Yes		No		Yes		No
	- Levetiracetam	Yes		No		Yes		No
	- Lorazepam	Yes		No		Yes		No
	- Oxcarbazepine	Yes		No		Yes		No
	- Phenobarbital	Yes		No		Yes		No
	- Phenytoin	Yes		No		Yes		No
	- Pregabalin	Yes		No		Yes		No
	- Topiramate	Yes		No		Yes		No
	- Tranxene	Yes		No		Yes		No
	- Valproic acid	Yes		No		Yes		No
	- Vigabatrin	Yes		No		Yes		No
	- Zonisamide	Yes		No		Yes		No
	Other medications:							
h)	Average dose (please specify medications and total units per day. e.g. mg, ml, etc.)							
i)	Average course of treatment							
	- age (in months) when treatment was started:							
	- age (in months) when treatment was stopped:							
	- if you use currently, list total number of months to date							
j)	What the effect on seizures?							
	- Seizure free					Yes		No

	- Greatly improved	Yes		No	
	- Slight improvement	Yes		No	
	- No effect	Yes		No	
	- Worse	Yes		No	
	Other (please specify):				
k)	Any improvements? (Please describe, if no, please indicate			No	
l)	What combinations of medications do you use?				
m)	what medications and combinations are most effective?				
n)	Which medication had the side effects (if any), and what were those effects? Please describe, if no, please indicate			No	
o)	If your child is now seizure free and off medication, please describe for how long:				
p)	Other treatments:				
	- surgery treatment (corpus callosotomy or other)	Yes		No	
	- are you using dietary therapy?	Yes		No	
	- ketogenic diet	Yes		No	
	- low glycemic index diet	Yes		No	
	- vagal nerve stimulator	Yes		No	
	- what is the effect? Please describe, if no, please indicate			No	
	Please provide any additional information regarding seizures, medications or treatments that would provide a clearer understanding of seizures in your child:				

3.	**Heart abnormality**	Yes		No	
a)	Congenital heart diseases				

	Please choose the appropriate option, that you know.						
	- hypoplastic left heart syndrome	Don't know		Yes		No	
	- common truncus	Don't know		Yes		No	
	- interrupted aortic arch	Don't know		Yes		No	
	- transposition of great arteries	Don't know		Yes		No	
	- tetralogy of Fallot	Don't know		Yes		No	
	- pulmonary valve atresia	Don't know		Yes		No	
	- tricuspid valve atresia	Don't know		Yes		No	
	Others						
b)	Cardiac investigation:			Yes		No	
	- How many times						
	In neonatal period:	At what age?					
	- What was revealed?						
	In infancy:	At what age?					
	- What was diagnosed?						
	After 1 year:	At what age?					
	- What was diagnosed?						
4.	Brain abnormality			Yes		No	
a)	Cerebral anomaly *(Please choose the appropriate option, that you know)*						
	- hydrocephalus	Don't know		Yes		No	
	- intracranial hemorrhage	Don't know		Yes		No	
	- craniosynostosis	Don't know		Yes		No	
	- premature closure of sutures	Don't know		Yes		No	
	- encephalocele	Don't know		Yes		No	
	- spina bifida	Don't know		Yes		No	
	- cephalohematoma	Don't know		Yes		No	

	- microcephaly/ macrocephaly	Don't know		Yes		No		
	Others							
	Cerebral MRI:							
	- How many times?							
	In neonatal period:	At what age?						
	- What was revealed?							
	In infancy:	At what age?						
	- What was diagnosed?							
	After 1 year:							
	- What was diagnosed?	At what age?						
b)	Encephalography (EEG)							
	- How many times?							
	In neonatal period:	At what age?						
	- What was revealed?							
	In infancy:	At what age?						
	- What was diagnosed?							
	After 1 year:	At what age?						
	- What was diagnosed?							

5.	**Breathing problems**			Yes		No		
	Please choose the appropriate option, that you know							
a)	<u>In neonatal period</u> (first 4 weeks of life):							
	- difficulty breathing at birth that gets progressively worse	Don't know		Yes		No		
	- periods of absent breathing for 20 seconds or longer	Don't know		Yes		No		
	- sleep-related breathing problems	Don't know		Yes		No		
	- rapid breathing	Don't know		Yes		No		
	- flaring of the nostrils	Don't know		Yes		No		
	- grunting sounds with breathing	Don't know		Yes		No		
	- pulling in at the ribs and sternum during breathing	Don't know		Yes		No		

	- chest retractions	Don't know		Yes		No	
	- blue coloring	Don't know		Yes		No	
	- continued need for mechanical ventilation, oxygen, or endotracheal tube	Don't know		Yes		No	
	- recurrent lung infections	Don't know		Yes		No	
b)	<u>In infancy</u> (from 1 month to 1 year):						
	- continued abnormal respirations	Don't know		Yes		No	
	- periods of absent breathing for 20 seconds or longer	Don't know		Yes		No	
	- continued need for mechanical ventilation or oxygen	Don't know		Yes		No	
	- sleep-related breathing problems	Don't know		Yes		No	
	- blue coloring	Don't know		Yes		No	
	- severe asthma	Don't know		Yes		No	
	- recurrent lung infections	Don't know		Yes		No	
	- bronchiectasis	Don't know		Yes		No	
	- childhood interstitial lung disease	Don't know		Yes		No	
	- pulmonary hypertension and other pulmonary vascular diseases	Don't know		Yes		No	
	- pneumothorax	Don't know		Yes		No	
c)	After 1 year:						
	- continued abnormal respirations	Don't know		Yes		No	
	- recurrent lung infections	Don't know		Yes		No	
	- severe asthma	Don't know		Yes		No	
	- progressive pulmonary diseases	Don't know		Yes		No	
e)	Lung examinations:			Yes		No	
	- How many times?						
	- At what age						

	- What was revealed	
	Please provide any additional information regarding another pulmonary disorders that you know and think as important:	

6.	**Ophthalmological disorders:**			Yes		No	
a)	Eye problems: *(Please choose the appropriate option, that you know)*						
	- visual impairment	Don't know		Yes		No	
	- blue sclera	Don't know		Yes		No	
	- strabismus	Don't know		Yes		No	
	- myopia/hyperopia	Don't know		Yes		No	
	- congenital cataract	Don't know		Yes		No	
	- retinoblastoma	Don't know		Yes		No	
	- retinopathy of prematurity	Don't know		Yes		No	
b)	Eye examinations:			Yes		No	
	- how many times?						
	- at what age						
	- what was revealed						
	Please provide any additional information regarding another ophthalmological disorders that you may additionally find important.						

7.	**Digestive system disorders:**			**Yes**		**No**	
a)	Gastrointestinal abnormality *(Please choose the appropriate option, that you know)*						
	- esophageal atresia/tracheoesophageal fistula	Don't know		Yes		No	
	- large intestinal atresia/stenosis	Don't know		Yes		No	

	- anorectal atresia/stenosis	Don't know		Yes		No	
	- omphalocele	Don't know		Yes		No	
	- gastroschisis	Don't know		Yes		No	
	Other:						
b)	Digestive system investigation			Yes		No	
	- which ones?						
	- how many times?						
	- at what age?						
	- what was revealed?						
c)	Digestive system problems:			Yes		No	
	- the child keeps refusing feeds or continues to vomit up feeds			Yes		No	
	- food aversion			Yes		No	
	- constipation			Yes		No	
	- food allergy			Yes		No	
	- malnutrition and insufficient weight gain			Yes		No	
	- obesity			Yes		No	
	Please provide any additional information regarding another digestive system problems, that you know and think as important:						

8.	**Hearing impairment**	Yes		No	
9.	**Skeletal anomalies:**	Yes		No	
	Please choose the appropriate option, that you know:				
	- reduction defects of upper and lower limbs	Yes		No	
	- talipes equinovarus/club foot	Yes		No	
	other limb deficiencies				
	- was an x-ray performed?	Yes		No	
	- how many times?				
	- what anomaly was determined after birth:				

	- in infant:					
	- after 1 year:					
10.	**Frequent infections**		Yes		No	
	- how often do colds occur?					
	- what kind?					
	- what treatment?					
	- the severity of the main symptoms depends on the presence / absence of concomitant diseases and their treatment?		Yes		No	
	- how exactly?					

11.	**Treatment:**					
	What methods of treatment do you currently use, or have you used in the past?					
a)	Physiotherapy/Physical Therapy		Yes		No	
	- What kind?					
	- How often?					
	What is the effect?					
	- Greatly improved		Yes		No	
	- Slightly improvement		Yes		No	
	- No effect		Yes		No	
	- Worse		Yes		No	
	Other:					
b)	Speech therapy		Yes		No	
	- What kind?					
	- How often?					
	- What is the effect?					
	Greatly improved		Yes		No	
	Slightly improvement		Yes		No	
	No effect		Yes		No	
	Worse		Yes		No	
	Other:					
c)	Other methods of therapy (please describe if this is applicable)					

12.	**Tumor medical history:**				
a)	Has anyone in the family (parents, grandparents, siblings, aunts, uncles) been diagnosed with any type of tumor?	Yes		No	
	-if yes, which type of tumor was diagnosed and at what age the diagnosis was made				
b)	Has the DHX30-afected individual developed any type of tumor?	Yes		No	
	- if yes, which type of tumor was diagnosed and at what age the diagnosis was made				
12.	What previous genetic studies have been done? (Select all that apply)				
a)	Karyotyping	Yes		No	
b)	Chromosomal microarray analysis (Array-CGH)	Yes		No	
c)	SNP-array	Yes		No	
d)	Metabolic screening	Yes		No	
e)	DNA analysis of CGG repeat	Yes		No	
f)	Gene panel analysis	Yes		No	
g)	Whole-exome sequencing (WES)	Yes		No	
h)	Others:				

We would be extremely grateful if you would be willing to share the results of genetic testing as well as any other medical records that you may have with us.

Please do send these to: o.ielesicheva@salk.at

With our signature, we confirm the following:

- We understood that participation in this Natural history study is voluntary.
- We agree that the results about the person for whom we are legally responsible may be used in anonymous form for scientific publications or presentations at scientific congresses.

The clinical information will be presented without mentioning any names, Dr. Olean Ielesicheva and Prof. Davor Lessel will make every effort to maintain anonymity.

- We are aware that anonymized data once published in a scientific journal cannot be withdrawn.

_____ _____

Town/City Date Signature