

Project 3: Genotype and Clinical Outcome in Conotruncal Defects

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Overall Goals

- Decipher the genetic contribution to the etiology of conotruncal defects
- Impact of genotype on clinical outcome

Specific Aims

1. Investigate the role of *NKX2.5* and its molecular partners in the etiology of conotruncal defects
2. Investigate whether subset of D-TGA and DORV share a common genetic etiology with heterotaxy syndrome
3. Impact of genotype on clinical outcome

1. Molecular Partners of *NKX2.5*: *TBX5*

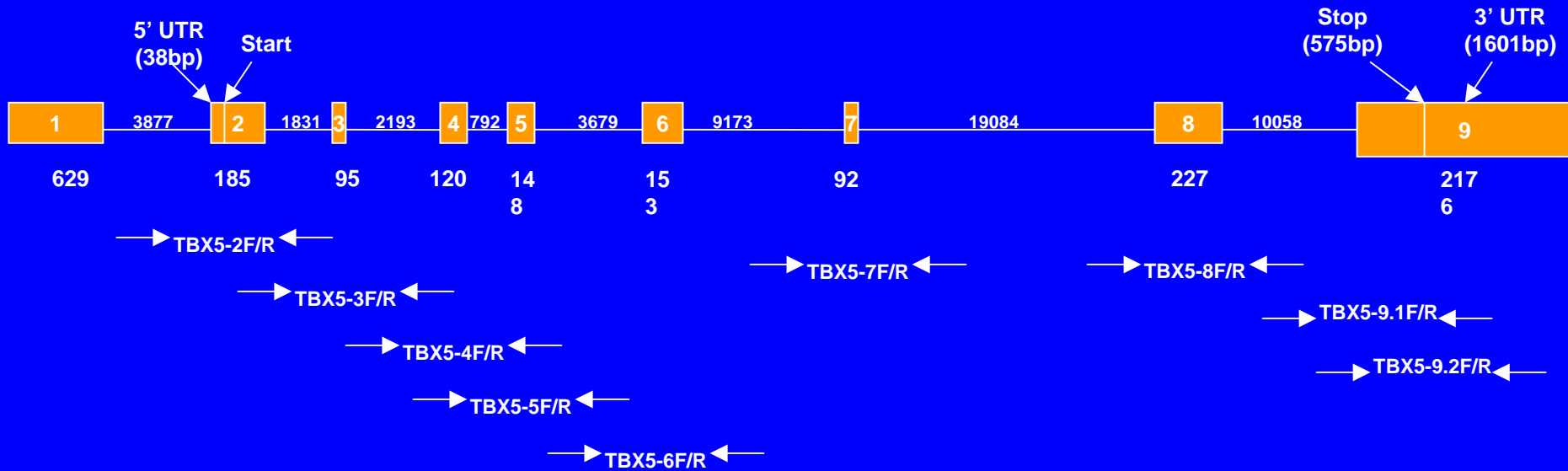
- Member of the T-box family
- Disease gene for Holt-Oram syndrome
 - Forelimb anomalies
 - Cardiac defects: ASD, VSD, TOF, HLHS, conduction anomalies
- Molecular partner of *NKX2.5* and *GATA4* though few known target genes
- Transcriptional promoter of cardiac specification and chamber morphogenesis and differentiation

Patient Population (N= 605)

Diagnosis	# Subjects
ASD	127
VSD	32
TOF	129
IAA	5
Truncus	17
HLHS	164
VAS	49
Coarc	82

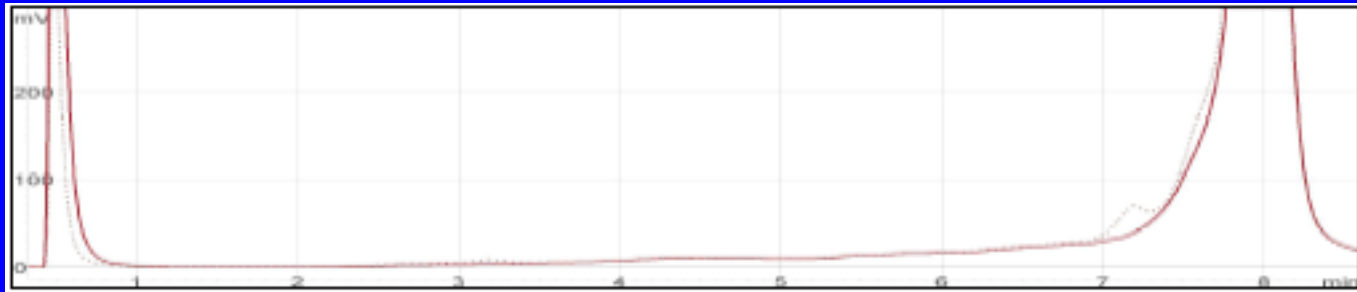
T-BOX 5 Gene

TBX5: Exons: 9 Transcript length: 3,825 bps Translation length: 518 residues

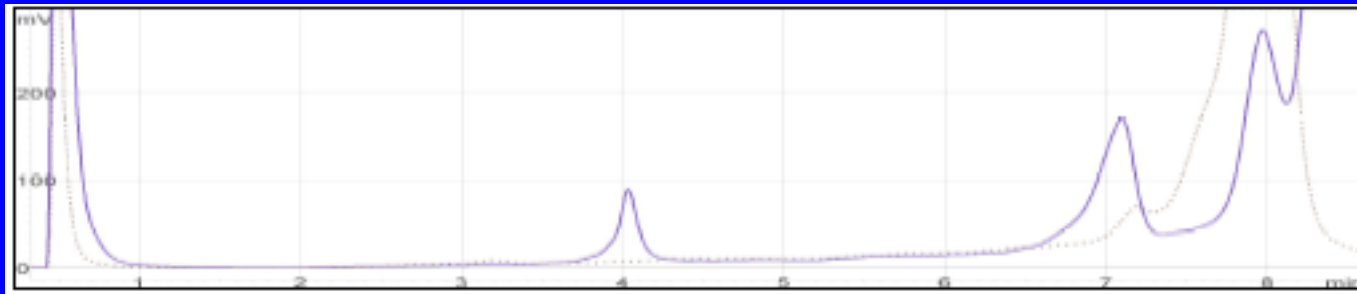


April 12, 2006

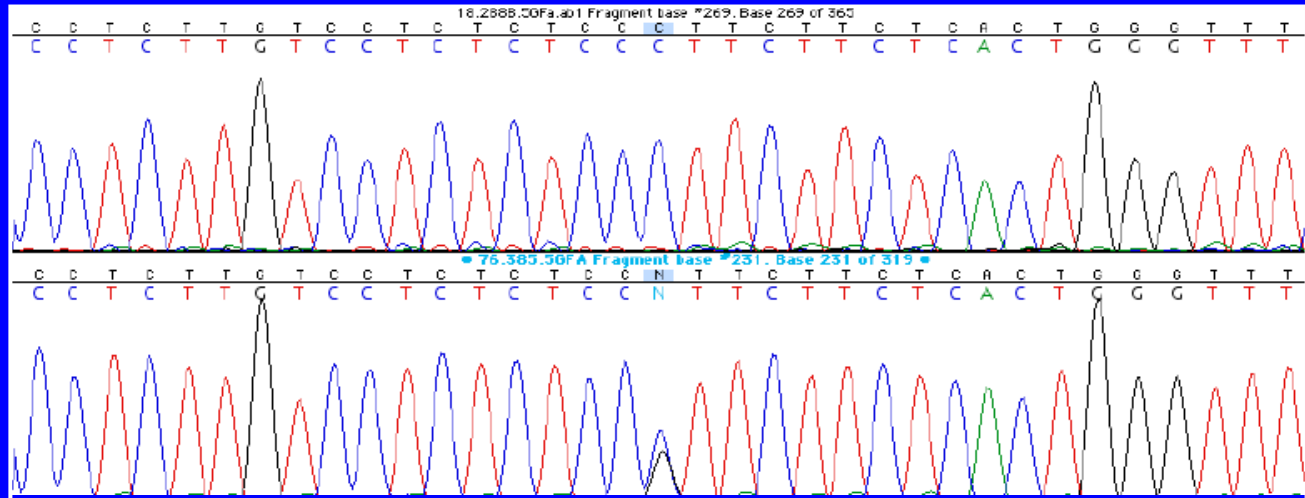
Control



Patient Sample



Sequencing

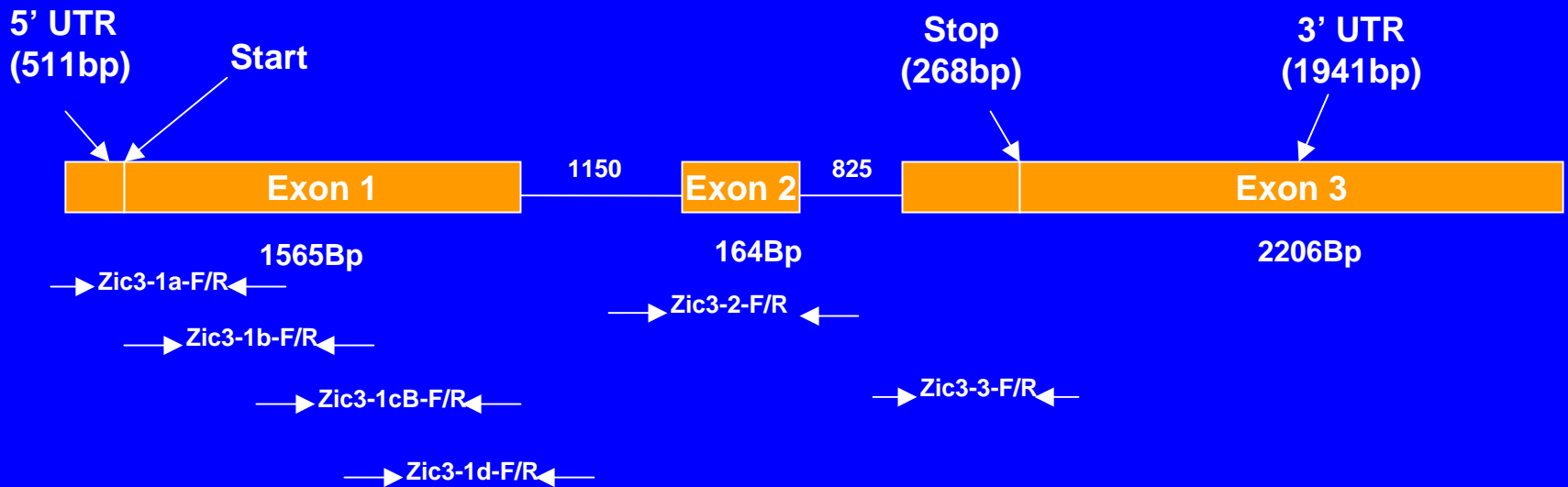


2. DORV / D-TGA: ZIC3

- Zinc finger transcription factor participating in left-right asymmetry
- Disease gene for X-linked heterotaxy
 - Some with CHD without laterality defects
- Heterotaxy characterized by DORV and TGA

ZINC FINGER PROTEIN OF CEREBELLUM, 3

ZIC3: Exons: 3 Transcript length: 3,935 bps Translation length: 467 residues



Patient Population

Diagnosis	# Subjects
DORV	70
D-TGA	77

3. Impact of Genotype on Clinical Outcome

- Analyze relationship between genotype and each of the following phenotypes:
 - a. Cardiac anatomy
 - b. Operative outcome
 - c. Intermediate outcome
 - d. Intermediate cardiovascular status: cross sectional analysis

Study Subjects: Inclusion Criteria

- 1° Cohort: Tetralogy of Fallot
 - 22q11 deletion
 - Trisomy 21
 - JAG1 mutation
 - No identified syndrome/genetic alteration
- 2° Cohort: IAA or truncus:
 - 22q11 deletion
 - No identified syndrome/genetic alteration

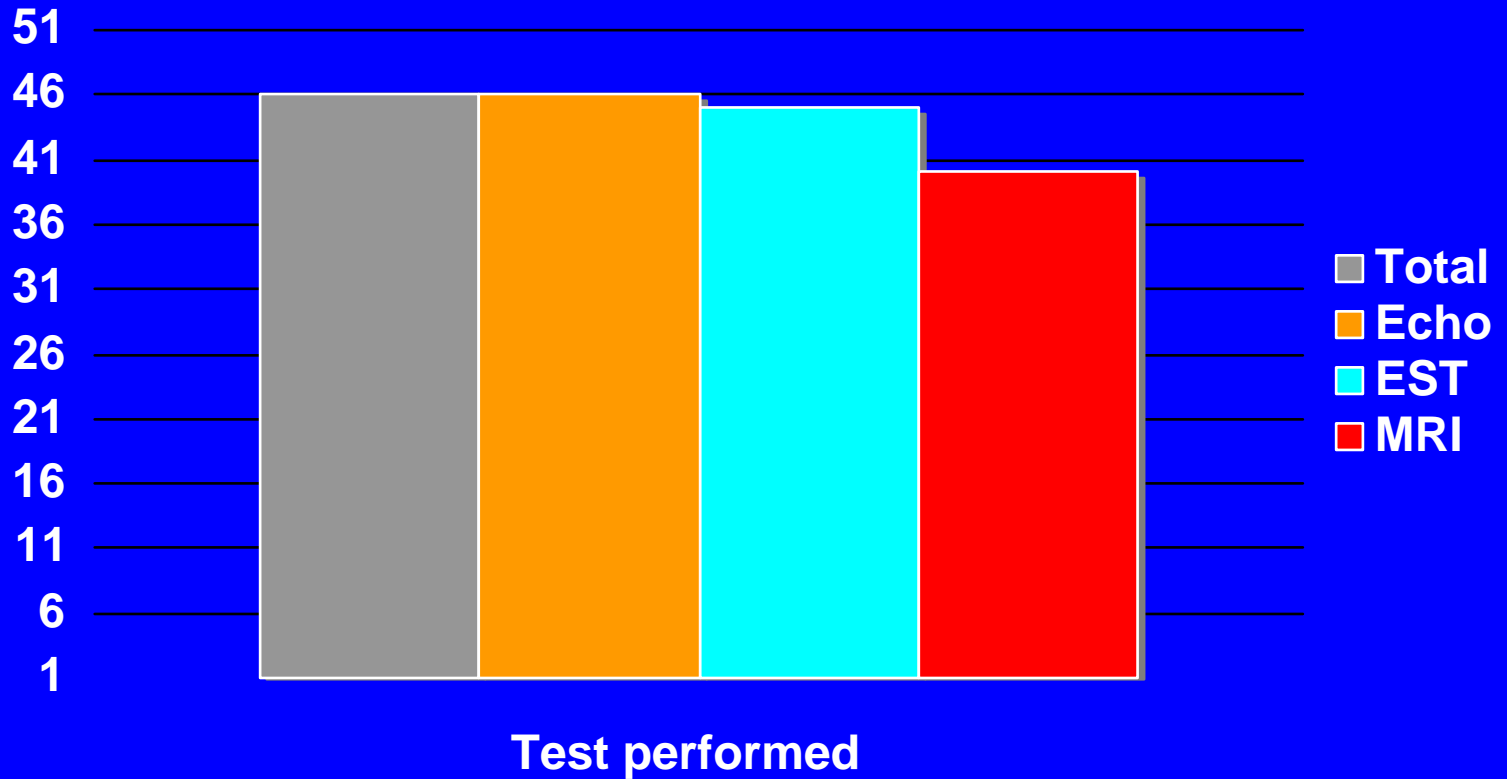
Personnel for Aim 3

- Investigators:
 - Betsy Goldmuntz, P.I.
 - Ronn Tanel, EP
 - Jack Rychik, Echo
 - Mark Fogel, MRI
 - Steve Paridon, EST
 - Jack Rome, Cath
- Support Staff
 - Research Nurses (Tina Hayden and Mei Lin Chen-Lim)
 - Data coordinator (Sharon Edman)
 - Biostats core (Chuck and crew)

Aim 3d: Progress to Date

	Total (%)
Letters sent	248
Unable to contact	51 (21%)
Declined	33 (13%)
Future	24
Pending	75
Participants (completed)	46 (19%)
Participants (scheduled)	10
Participants (total)	56 (23%)

Tests Performed to Date



Database

- Revision of previous case report forms:
 - Demographics
 - Birth/pregnancy/family history (Progeny)
 - Genetics examination
 - Extracardiac and Cardiac
 - Cytogenetics
- Transfer of early SCCOR data into Clintrials platform
- Develop new Case Report Forms for Operative and Cross Sectional Study
 - Daily and operative forms (3b)
 - Echo, EST, MRI, EP, Cath, medical history (3d), QOL