Deep Learning Models for Quantifying Testicular Toxicity in Rats

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Erio Barale-Thomas[2] • Fauve Versaevel[2] • Fetene Tekle[3] • Pranab Samanta[1] • Rohit Garg[1] • Tijo Thomas[1] • Uttara Joshi[1]

[1] Aira Matrix, Mumbai, India • [2] Preclinical Sciences & Translational Safety – Janssen R&D, Beerse, Belgium • [3] Statistics & Decision Sciences – Janssen R&D, Beerse, Belgium (corresponding author: ebarale@its.jnj.com)

INTRODUCTION

Recognizing the 14 stages in the rat testis cycle is a difficult task [1] (fig. 1). We [2] have developed a deep learning (DL) based method to automate the staging which is easy to use, and provide results comparable to an expert on normal testes, and to historical data [3]. Taking this ahead, we propose a DL-based method for identification and quantification of findings in rat testes.

We have concentrated on a subset of findings from the INHAND nomenclature [4]. We selected several Janssen toxicology studies on which early stages findings (spermatid retention after 1 month) and more chronic, degenerative findings were recorded (table 1).

We developed DL models to detect those findings and we compared them to the pathologist's results (table 2).

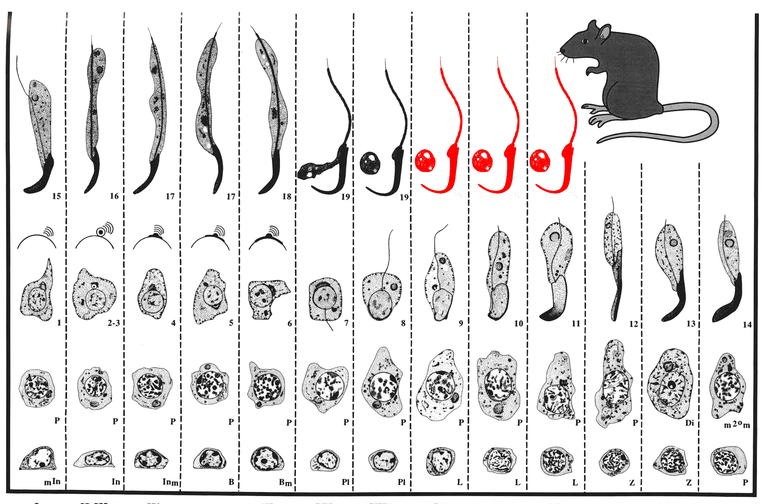


Fig. 1. The cycle stage [3] showing the cell associations. For example, in stage VIII, there are preleptotene and pachytene spermatocytes, round spermatid (step 8) and a mature elongated spermatid step 19 being released. In stages IX-XI, the spermatid retention is symbolized by presence of unreleased last step mature spermatid (in red)

Atrophy, Leydig Cell	**Multinucleated Giant Cells**
Atrophy, Tubular	Necrosis, Leydig Cell
Degeneration, Germ Cell	**Necrosis, Testis**
Degeneration, Tubular	**Necrosis, Tubular**
Degeneration/Atrophy, Tubular	Residual Bodies, Atypical
Dilatation Rete Testis	**Retention, Spermatid**
Dilatation, Tubular	Vacuolation Leydig Cell
Hyperplasia, Leydig Cell	**Vacuolation, Tubular**

Table 1. List of INHAND terms for the testis [4]. In bold, the findings for which the DL models were developed

Group / Animal	Spermatid retention	Degeneration, germ cell	Vacuolation, tubular	Atrophy, tubular	Degeneration, tubular	Dilatation, tubular
1M2	0	0	0	5 u	2 u	2 u
4M31	3	4	1	2 u	0	0
4M32	2	2	0	0	0	0
4M33	2	2	0	0	0	0
4M34	0	1	0	0	0	0
4M38	0	1	0	0	0	0
4M39	0	1	0	0	0	0

Table 2. Example of descriptive/semi-quantitative results generated by the pathologist. Study Y (3 months); animals 1, 3-10, 35-37 & 40 were normal and are not reported in the table. (u: unilateral)

MANUAL METHOD & DESIGN OF THE ALGORITHMS

We have trained various deep learning networks by using Hist-Net, Efficient-Net and YAMU-Net based architectures by training on 512x512 tiles from abnormal images having the abnormalities viz. tubular degeneration, tubular dilatation, degeneration/necrosis, vacuolation, multinucleated giant cell and spermatid retention [5,6] (fig. 2, 3, table 3).

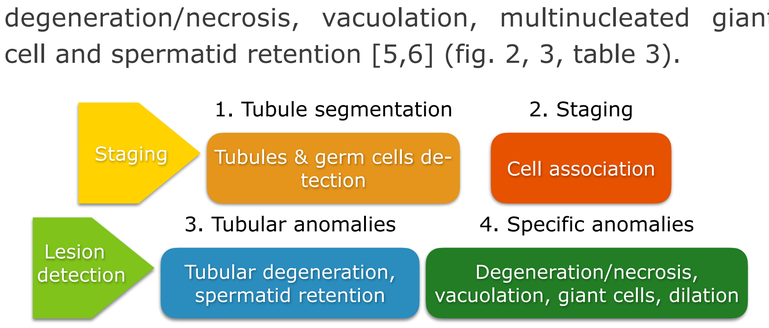


Fig. 2. Solution approach: algorithm workflow

A rule-based approach was followed for detecting stage-specific abnormalities viz. spermatid retention and degeneration/necrosis of spermatids. Then, we calculated the percentage of affected tubules with respect to total tubules present in the testis.

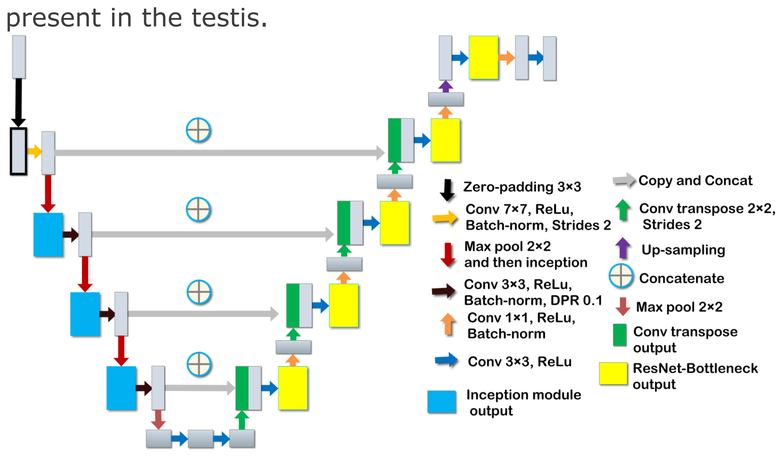


Fig. 3. Hist-Net Architecture used for segmentation tasks

For validation, slide level findings provided by pathologists on data from two studies (X, 1 month and Y, 3 months) were compared with algorithm results, and statistical analysis was performed.

Findings	Network Details
Germ cells (Round Spermatids, Elongated Spermatids, Meiotic Bodies, Round Spermatids in Stage X, Spermatogonia, Spermatocytes)	**HistNet, YAMU-Net**
Degeneration/Necrosis	**HistNet, EfficientNet, YAMU-Net**
Degeneration, Tubular	**Histnet**
Vacuolation, Tubular	**YAMU-Net**
Multinucleated Giant Cells	**EfficientNet**

Table 3. CNN selected depending on the finding

RESULTS

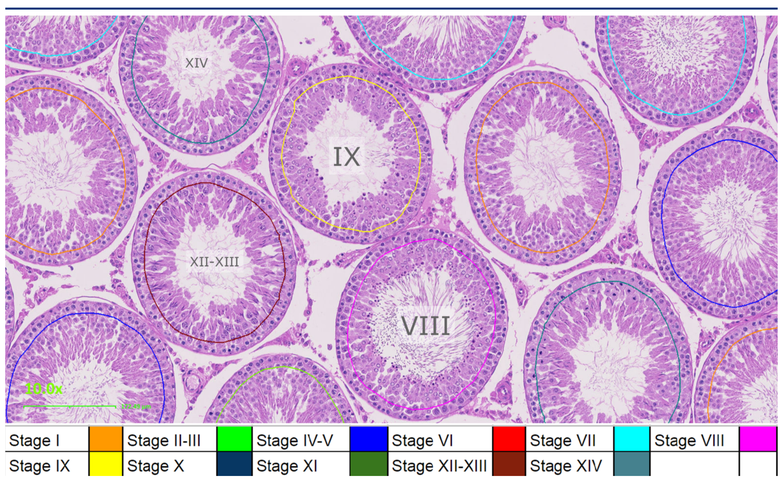
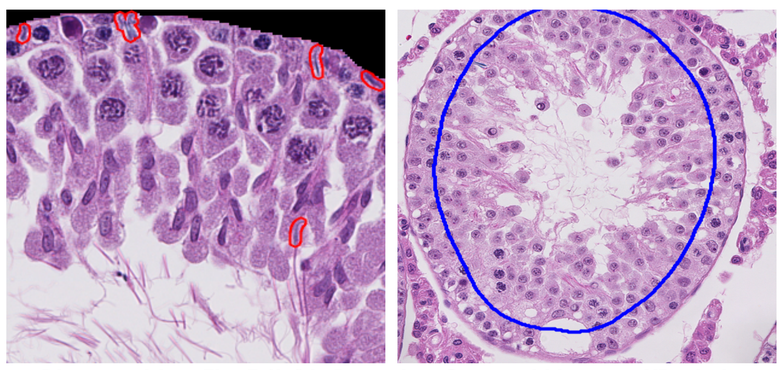
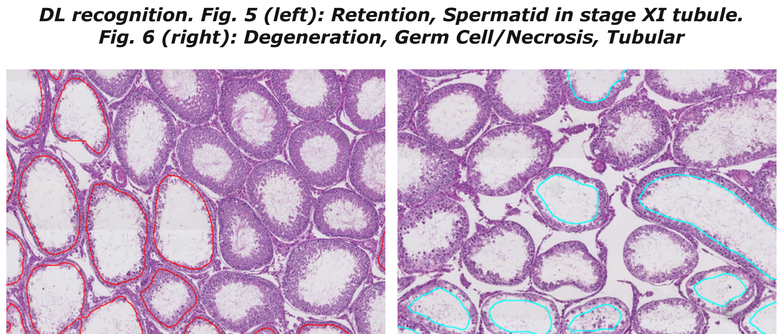


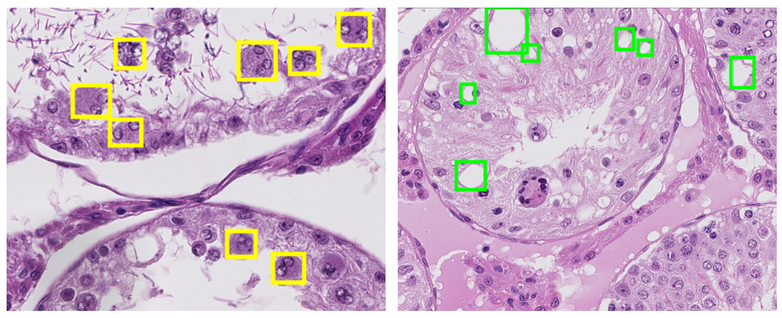
Fig. 4. DL recognition of testis tubules and stages / group of stages. There was a perfect concordance between the historical stage frequency reported in [2], and the stage frequency in the study [3] as assessed by an expert and by the current stage-detection DL model



DL recognition. Fig. 5 (left): Retention, Spermatid in stage XI tubule. Fig. 6 (right): Degeneration, Germ Cell/Necrosis, Tubular



DL recognition. Fig. 7 (left): Degeneration, Tubular. Fig. 8 (right): Dilatation, Tubular



DL recognition. Fig. 9 (left): Multinucleated Giant Cells. Fig. 10 (right): Vacuolation, Tubular

COMPARING MANUAL & DL RESULTS

Quantitative outputs of the algorithm correlate with semi-quantitative grades provided by the pathologist (table 4, 5). The proposed method can accurately detect and quantify spermatid retention, degenerative tubules, atrophic testes and other findings in normal or abnormal testes (table 6).

Study/ animal	Group	# Tubules	# Tubules with spermatid retention	% Tubules with spermatid retention	Janssen R&D reports*
X 46	4	503	98	19.5	P
X 44	4	404	81	20.0	P
Y 32	3	611	91	14.9	2
Y 33	3	601	98	16.3	2
Y 31	3	624	130	20.8	3
Y 21	2	635	137	21.6	3

* P: present, not graded; 2: mild; 3: moderate (on a severity scale of 5)

Table 4. DL AND pathologist's assessment of spermatid retention in studies X (1 month) and Y (3 months). Extract of unilateral results (except untreated group 1 animal 13, which show an incidental tubular degeneration in 1 testis) sorted by increasing %

Study/ animal	Group	# Tubules	# Degenerated tubules	% Degenerated tubules	Janssen R&D reports*
X 44	4	404	0	0.0	0
X 13	1	500	1	0.2	0
X 13	1	415	77	18.6	4
Y 43	4	581	2	0.3	1
Y 45	4	652	561	86.0	4
Y 41	4	654	641	98.0	5
Y 46	4	545	538	98.7	5
Y 39	3	749	741	98.9	5
Y 38	3	739	735	99.5	5

* 0: no abnormality detected; 1: minimal; 4: marked; 5: severe (on a severity scale of 5)

Table 5. DL recognition of tubular degeneration/atrophy compared to the pathologist's assessment in studies X (1 month) and Y (3 months). Extract of unilateral results sorted by increasing %

Parameter Name	Accuracy	Sensitivity	Specificity
Degeneration, Tubular	100.0	100.0	100
Necrosis, Tubular	94.4	70.0	97.4
Retention, Spermatid	97.8	100.0	97.1
Vacuolation, Tubular	95.5	100.0	95.3
Dilatation, Tubular	100.0	100.0	100

Table 6. Performance parameters of the AI models

CONCLUSION

The DL method to quantify stage frequencies in H&E slides was easier and quicker than manual staging, and was in accordance with published material and with the pathologist's results. It also performed well on abnormal testes.

The DL methods to detect and quantify findings like spermatid retention, vacuolation and degeneration changes also correlated well with the pathologist's grading, with a better sensitivity.

We are preparing future developments to identify other abnormalities and generalise the method to other species (dogs, mouse, NHP).

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