Development of database of genes related to Endometriosis

Project report submitted in fulfillment of the requirement for the degree of Bachelor of Technology

In

BIOINFORMATICS

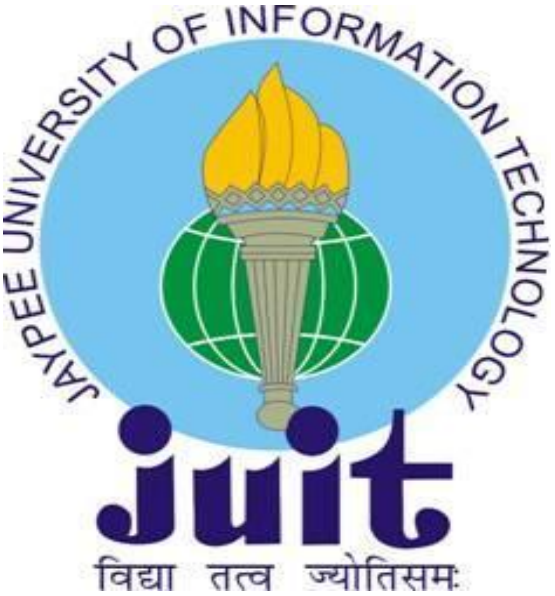
by

Deeksha Pandey (131514)

Under the supervision of

Dr. Jayashree Ramana

To



Department of Biotechnology and Bioinformatics

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BONAFIDE CERTIFICATE

This is to certify that this project report entitled ***"Development of database of genes related to Endometriosis",*** submitted to Jaypee University of Information Technology, Waknaghat, Solan, is a bonafide record of work done by ***"Deeksha Pandey"*** for the degree of B.Tech Bioinformatics has been carried out under my supervision.

Dr. Jayashree Ramana,
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Jaypee University of Information Technology,
Waknaghat, Solan, H.P
Dated:

DECLARATION BY THE AUTHOR

This is to affirm this report titled ***"Development of database of genes related to Endometriosis"*** has been written by me, i.e. Deeksha Pandey, under the supervision of Dr. Jayashree Ramana. No part of report has been plagiarized from other sources and all the information used from other sources has been acknowledged. I aver that if any part of this report is found to be plagiarized, I shall take full responsibility of it.

Deeksha Pandey
(131514)

ACKNOWLEDGEMENT

I owe my profound gratitude to my project supervisor ***Dr. Jayashree Ramana***, who took keen interest and guided me all along in my project work titled **—** ***Development of database of genes related to Endometriosis***, till the completion of my project by providing all the necessary information for developing the project. The project development helped me in understanding the disease better and inspired me to work in order to help in any further research. I'm really thankful to her.

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Abstract

Endometriosis has become one of the major concerns in the current times, it may or may not be cancerous and to understand the functioning of the endometriotic condition we need to understand the genetic predisposition of this condition of endometriosis.

So, in order to understand the genetic predisposition, a database will be developed that will include all the genes that may be resulting in endometriosis and these genes will later be analyzed based on their functioning and abundance in various case studies.

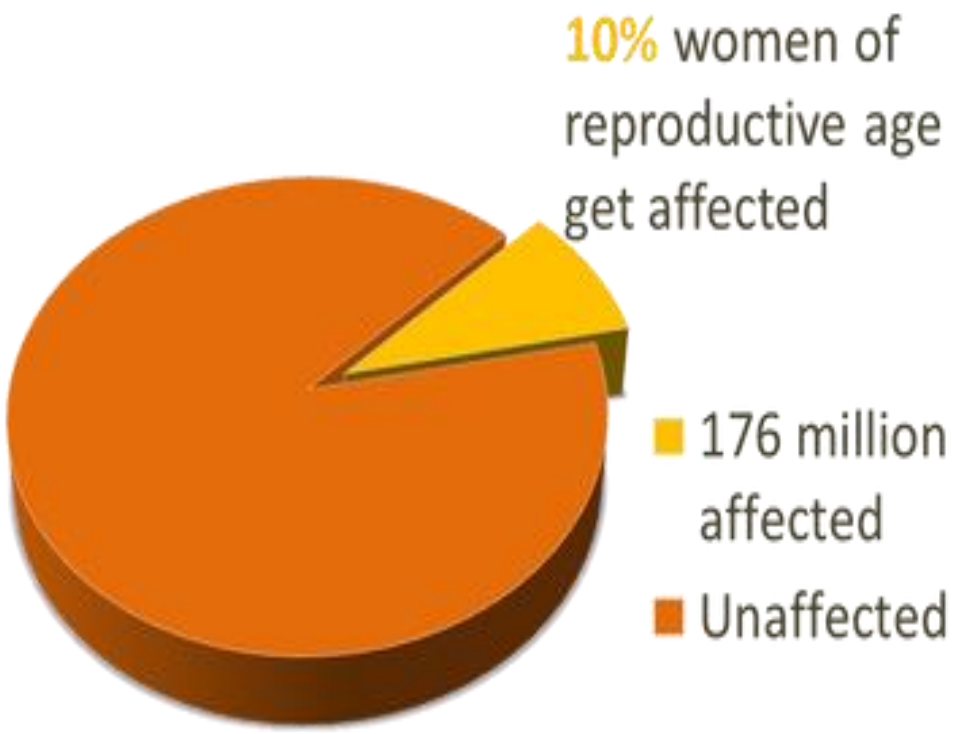


Fig 1. Pie chart

INTRODUCTION
OVERVIEW

In the condition of endometriosis, a layer of tissue generally covering the internal part of the female reproductive organ grows outside of it. The main organs affected are ovaries, fallopian tubes, the tissues around the uterine lining, in the very rare cases it is noticed in the other parts of the female body. The women suffering from it feels the pelvic pain.

The fifty percent of the patients suffer from pelvic pain along with the pain during their periods. Painful sexual intercourse is also reported in the patients suffering.
The symptoms that usually get neglected include bowel symptoms. Approximately 25% of patients don't show any type of symptoms.

Even with the endometriosis, the tissues act normal they get thick, break down and dispose with period blood every month.

When it effects ovaries, cysts that form are called endometriomas.
.
It can cause severe pain during menstruation.

It's believed that it can have social and psychological effects.
Although the cause is not entirely clear but we can visualize family history of the condition in various cases.
The tissue growths due to endometriosis are not cancer. (Although there are some cancerous cases also reported but in general it's not cancer)

Biopsy is the method used for diagnosis.
The few things that are believed to help with endometriosis include pain medication, hormonal treatments and surgery.

Tentative evidences suggested that the regular use of oral contraceptives does help to reduce the risk of endometriosis.

SYMPTOMS

The primary symptom of the endometriosis is pelvic pain, often associated with menstrual period. Although many women experiences cramping during their menstrual period, women with endometriosis typically describe menstrual pain that's far worse than usual. They also tend to report that the pain increases over time.

Common signs and symptoms of endometriosis may include:

- **Painful periods (dysmenorrhea).** Pelvic pain and cramping begins before the starting of menstrual cycle and continues for several days during the cycle, women also have lower back pain as well as abdominal pain.
- **Pain during sex.** Pain during the intercourse or after sex is quite common in case of endometriosis.
- **Pain while bowel movements /urination.** Women are likely to experience pain while urination during the period.
- **Excessive bleeding during menstrual cycle.** Women experience occasional heavy periods (menorrhagia) or bleeding between periods (menometrorrhagia) in such cases.
- **Infertility.** Endometriosis causes infertility in most of the cases.
- **Other symptoms.** Apart from these one may experience fatigue, diarrhea, constipation, bloating or nausea during menstrual periods.

The severity of pain isn't necessarily a reliable source to tell the extent of the condition. Since a few women with mild endometriosis too have intense pain, while a few suffering with advanced endometriosis may experience a little pain or in some cases no pain at all.

Endometriosis can easily be mistaken for other conditions that are responsible for pelvic pain, such as pelvic inflammatory disease (PID) or ovarian cysts.

It's also confused with irritable bowel syndrome (IBS), IBS can accompany endometriosis in various cases, which complicates the diagnosis.

CAUSES

As we already know that the meticulous cause of the endometriosis is not very convincing, the possible explanations that can cause endometriosis includes:

- **Retrograde menstruation.** In retrograde menstruation, menstrual blood containing endometrial cells flows back through the fallopian tubes and into the pelvic cavity instead of out of the body. These displaced endometrial cells stick to the pelvic walls and surfaces of pelvic organs, where they grow and continue to thicken and bleed over the course of each menstrual cycle.
- **Transformation of peritoneal cells.** In what's known as the "induction theory," experts propose that hormones or immune factors promote transformation of peritoneal cells — cells that line the inner side of your abdomen — into endometrial cells.
- **Embryonic cell transformation.** Hormones such as estrogen may transform embryonic cells — cells in the earliest stages of development — into endometrial cell implants during puberty.
- **Surgical scar implantation.** After a surgery, such as a hysterectomy or C-section, endometrial cells may attach to a surgical incision.
- **Endometrial cells transport.** The blood vessels or tissue fluid (lymphatic) system may transport endometrial cells to other parts of the body.
- **Immune system disorder.** It's possible that a problem with the immune system may make the body unable to recognize and destroy endometrial tissue that's growing outside the uterus.

RISK FACTORS

Factors that cause the risk of developing the condition of endometriosis are as following:

- Not being able to give birth
- Getting the period at a very early age
- Getting the menopause at later stage of life than normal
- Comparative small menstrual cycles, that is lesser than the 27 days
- Production of higher amount of estrogen in the body
- Comparative lower body-mass-index
- If more than one blood relations (mother, aunt or sister) suffering with endometriosis
- Uterine abnormalities

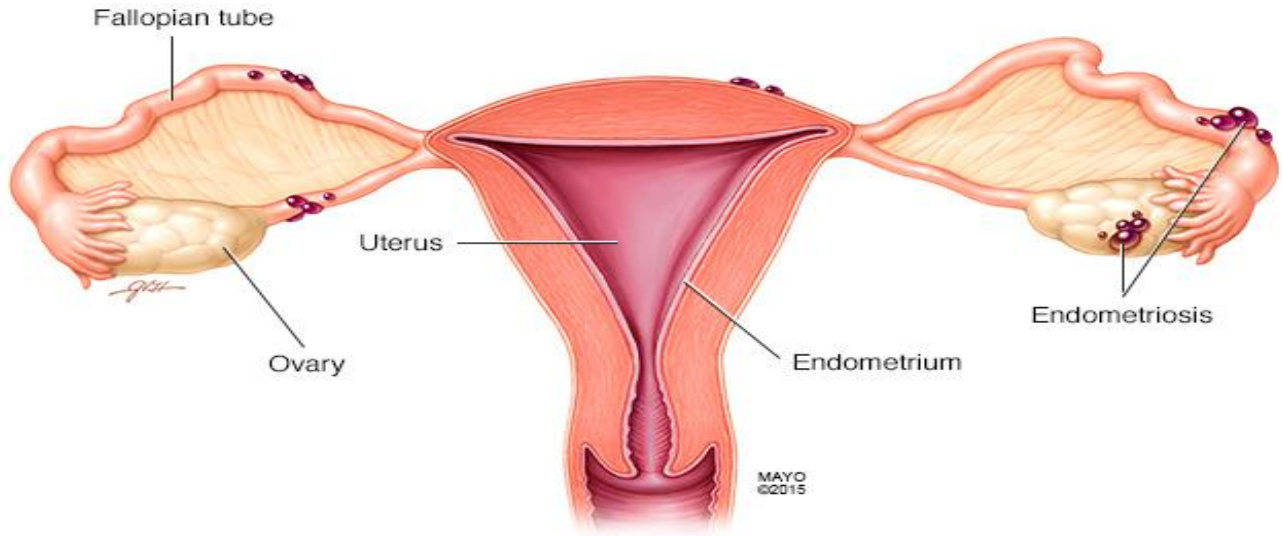


Fig 4.1- endometriotic sightings

COMPLICATIONS

Infertility

The top most complication due to the endometriosis is diminished fertility. Roughly around 1/3 to 1/2 of women suffering from the endometriosis face struggle in conceiving.

As it's known to conceive the baby, an egg must be unconstrained from one of the ovaries then it should travel through the fallopian tube so that it can be impregnated by a sperm cell and then it should attach the aforementioned to the uterus wall to begin developing as a fetus. The case of endometriosis barricades the fallopian tube thus hindering the egg and sperm from fusion.

But many of the women with mild and moderate endometriosis are still able to conceive and carry a pregnancy to the term.

Ovarian cancer

Ovarian cancer is oddly common in women with endometriosis.

Although in rare cases another type of cancer that is endometriosis-associated adenocarcinoma is reported to develop later in life in women who have had endometriosis.

STATISTICS AND HISTORY

As per a report endometriosis affected around 10.8 million women.

Another evaluation says that about 6–10% of women suffer with endometriosis.

It is commonly found with the age group of 30's to 40's, although it can commence in girls of even 8-years-old.

It does result in a few deaths every year.

Endometriosis was first determined to be an entirely separate condition/disease in the 1920s.

Before 1920s endometriosis and adenomyosis were considered to be the same.

Endometriosis was first discovered microscopically by Karl von Rokitansky in 1860.

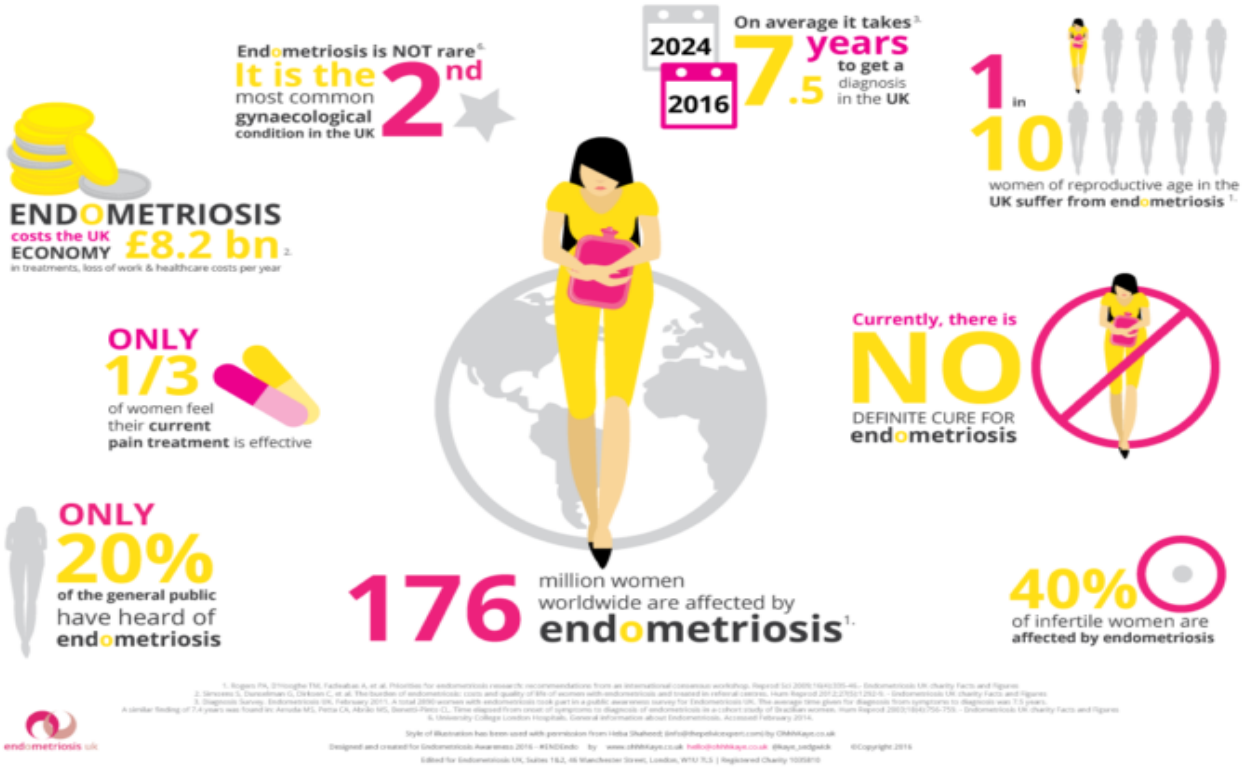
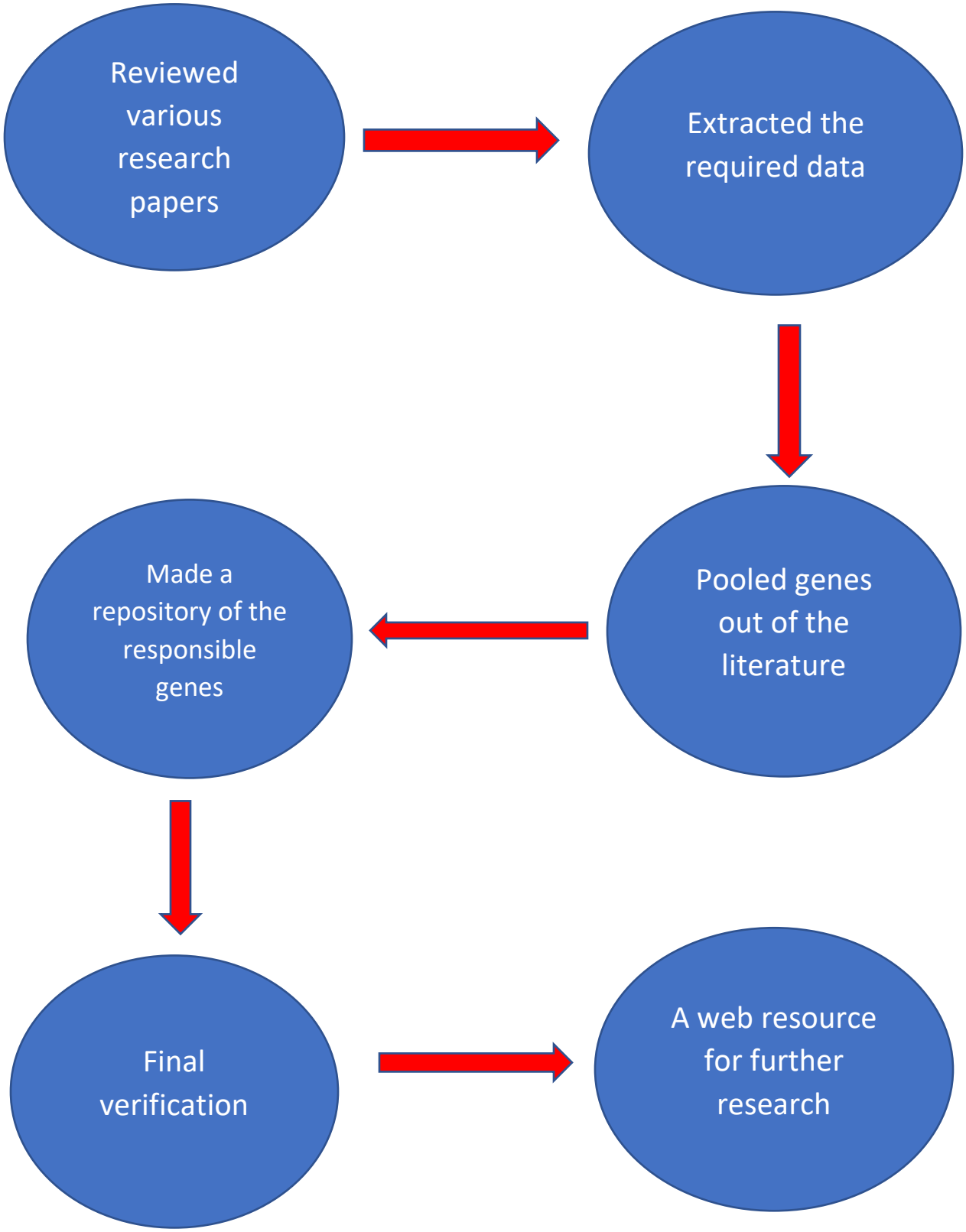


Fig 6.1

AIMS AND OBJECTIVES

1- All the genes related to the condition of endometriosis were collected from various literature and research articles and the database was developed.
2- A web-resource containing the repository of all genes specific to endometriosis was developed.

METHODOLOGY



First of all, I reviewed various research papers in order to understand the concept and functioning of endometriosis and then once reviewing various research papers I pooled out the genes responsible for endometriosis based on case studies and created a repository of these genes which are supposedly responsible for endometriosis.

This repository consists the genes, their official name, the pubmed id of the research paper they are taken from and their functions in respect to endometriosis.

Then these genes were verified and a web resource was developed.

To develop the web resource the requirements were as following,

The non-functional requirements:

- There should be sufficient network bandwidth
- Backup- provision for data backup
- Maintainability- easy to maintain
- Performance/ response time- fast response
- Usability by target user community- easy to use
- Expandability- needs to be future proof or upgradable
- Safety- should be safe to use

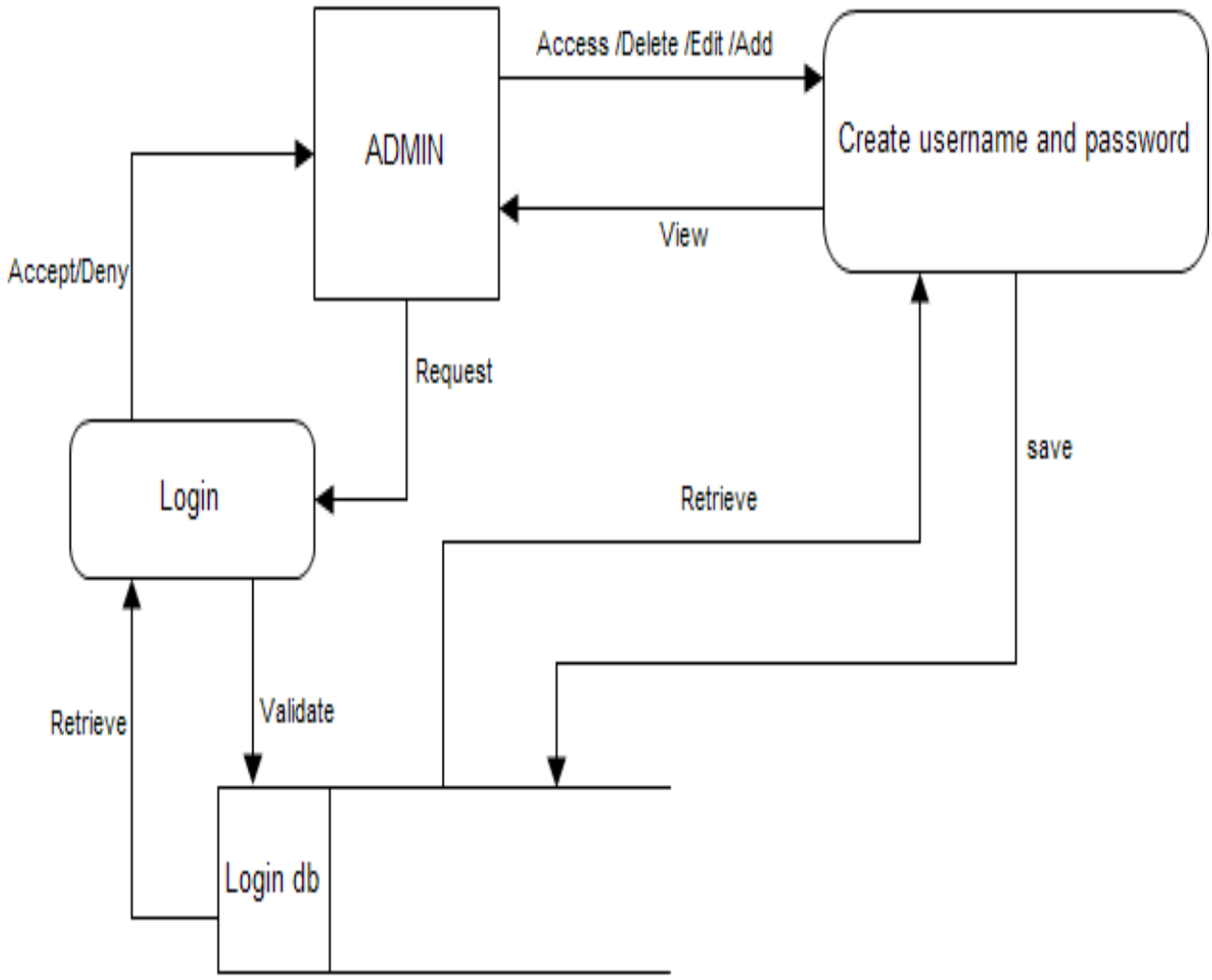
Hardware requirements:

- **Operating System:** Windows 7 and above.
- **Processor:** Intel dual core or above
- **Processor Speed:**1.0GHZ or above
- **RAM:** 1 GB RAM or above
- **Web Browser:** Google Chrome 29.0.1547 and above, Mozilla Firefox 1.7 and above.
- **Software Requirements:** Notepad, Xampp 5.1.28

Technologies used:

- HTML.
- CSS.
- JavaScript.
- Php.
- mySQL.

DATAFLOW DIAGRAM



Since the entire repository of 640 genes can't be displayed so first 80 genes are mentioned below

Serial no.	GENE	Official full name	PubMed ID	Gene ID	Function
1	EZH2	enhancer of zeste 2 polycomb repressive complex 2 subunit	28754964	2146	Induces epithelial-mesenchymal transition (EMT) in cancers
2	SIRT1	sirtuin 1	28754906	23411	known to regulate epigenetic gene silencing and suppress recombination of rDNA
3	BCL6	B-cell CLL/lymphoma 6	28754906	604	in eutopic endometrium of infertile women with endometriosis disorder leading to over-expression of the oncogene BCL6
4	KRAS	KRAS proto-oncogene, GTPase	28754906	3845	likely participate in the pathogenesis of endometriosis
5	(PGR)	progesterone receptor gene	28837027	5241	the genes related to endometrium-embryo interaction regulated by progesterone
6	HBEGF	heparin binding EGF like growth factor	28837027	1839	
7	ITGAV	integrin subunit alpha V	28837027	3685	
8	ITGB3	integrin subunit beta 3	28837027	3690	
9	SPP1	secreted phosphoprotein 1	28837027	6696	
10	GDF-9 gene	growth differentiation factor 9	28831646	2661	The encoded preproprotein is proteolytically processed to generate

					each subunit of the disulfide-linked homodimer. This protein regulates ovarian function. This complex binds to the anti-Mullerian hormone receptor type 2 and causes the regression of Mullerian ducts in the male embryo that would otherwise differentiate into the uterus and
11	AMH	anti-Mullerian hormone	28831646	268	fallopian tubes.
12	AMHR2	anti-Mullerian hormone type 2 receptor	28831646	269	prevents the development of the mullerian ducts into uterus and Fallopian tubes
13	17β-HSD1	hydroxysteroid 17-beta dehydrogenase 3	28800957	3293	
14	IL6R	Interleukin-6	28779573	3570	
15	PTGS2	prostaglandin-endoperoxide synthase 2	28734688	5743	plays a crucial role in the acquisition of oocyte competence
16	CCND1	cyclin D1	28720098	595	
17	ID2	inhibitor of DNA binding 2	28678915	3398	Increased expression in patients with endometriosis
18	PRELP	proline and arginine rich end leucine rich repeat protein	28678915	5549	Increased expression in patients with endometriosis
19	SMOC2	SPARC related modular calcium binding 2	28678915	64094	Increased expression in patients with endometriosis
20	FJX1	four jointed box 1	28673206	24147	Overexpression in Eutopic Endometrium From Women With Endometriosis.
21	KLF11	Kruppel like factor 11	289384	8462	Endometriosis related

			37		fibrosis is regulated epigenetically female fibrotic predilection was mediated by differential sex steroid regulation of
22	COL1A1	collagen type I alpha 1 chain	28938437	1277	KLF11/Collagen 1A1 (COL1A1) signaling
23	IL6	interleukin 6	28927243	3569	
24	XRCC1	X-ray repair cross complementing 1	28926725	7515	meta-analysis suggested that Arg399Gln in XRCC1 was associated with endometriosis risk
25	Ucn1	Urocortin	28925754	7349	detect pelvic endometriosis in symptomatic women have a statistically significantly different
26	LGR5	leucine rich repeat containing G protein-coupled receptor 5	28923287	8549	expression profile in deep-infiltrating endometriosis
27	TGF-β ligands	transforming growth factor beta 1	28903471	7040	TGF-β1 plays a major role in the development of peritoneal endometriosis lesions
28	P2RX3	purinergic receptor P2X 3	28898282	5024	results suggest that P2X3 might be involved in endometriosis pain signal transduction via ERK signal pathway
29	RHOJ	ras homolog family member J	28881265	57381	
30	C2	complement C2	28881265	717	
31	HLA-DRA	major histocompatibility complex, class II, DR alpha	28881265	3122	
32	CCL19	C-C motif chemokine ligand 19	28856757	6363	data indicate CCL19/CCR7 contributes to proliferation and

33	CCR7	C-C motif chemokine receptor 7	28856757	1236	invasion of ESCs, which are conducive to the pathogenesis of endometriosis throug h activating PI3K/Akt pathway. data indicate CCL19/CCR7 contributes to proliferation and invasion of ESCs, which are conducive to the pathogenesis of endometriosis throug h activating PI3K/Akt pathway.
34	CXCL12	C-X-C motif chemokine ligand 12	29161347	6387	Pharmacological blockage of the CXCR4-CXCL12 axis in endometriosis leads to contrasting effects in proliferation, migration and invasion.
35	CXCR4	C-X-C motif chemokine receptor 4	29161347	7852	Pharmacological blockage of the CXCR4-CXCL12 axis in endometriosis leads to contrasting effects in proliferation, migration and invasion.
36	miR-122	microRNA 122	29149541	406906	Serum miR-122 and miR-199a were significantly increased in endometriosis, indicating that these microRNAs might serve as biomarkers for the diagnosis of endometriosis.
37	miR-199a	microRNA 199a-1	29149541	406976	Serum miR-122 and miR-199a were significantly increased in endometriosis,

38	ARID1A	AT-rich interaction domain 1A	29135119	8289	indicating that these microRNAs might serve as biomarkers for the diagnosis of endometriosis. The decreased gene and protein expression levels of ARID1A are related to the occurrence and development of endometriosis-associated ovarian cancer, especially OCCC.
39	CYP2C19	cytochrome P450 family 2 subfamily C member 19	29102810	1557	study suggest that CYP2C19*2 is positively associated with endometriosis and that BMI may have a significant interaction with CYP2C19*2 and the risk of endometriosis.
40	MIR200C	microRNA 200c	29116025	406985	The MALAT1/miR-200c sponge may be a potential therapeutic target for endometriosis
41	MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	29116025	378938	The MALAT1/miR-200c sponge may be a potential therapeutic target for endometriosis
42	ZEB1	zinc finger E-box binding homeobox 1	29116025	6935	The MALAT1/miR-200c sponge may be a potential therapeutic target for endometriosis
43	ZEB2	zinc finger E-box binding homeobox 2	29116025	9839	The MALAT1/miR-200c sponge may be a potential therapeutic target for endometriosis
44	FEN1	Flap Endonuclease 1	29109095	2237	The FEN1 rs174538 A allele is a novel protective biomarker for endometriosis and

					this genotype may have interactions with age- and hormone-related factors on the development of endometriosis. It seems that the aberrant activation of Wnt/β-catenin signaling in the secretory phase of the menstrual cycle in endometriosis has two essential elements: excessive inactivation of GSK-3β and suppression of the expression of Wnt signaling inhibitor
45	WNT7a	Wnt family member 7A	291078 40	7476	DKK-1
46	DKK-1	dickkopf WNT signaling pathway inhibitor 1	291078 40	22943	It seems that the aberrant activation of Wnt/β-catenin signaling in the secretory phase of the menstrual cycle in endometriosis has two essential elements: excessive inactivation of GSK-3β and suppression of the expression of Wnt signaling inhibitor DKK-1
47	CTNNBIP1	catenin beta interacting protein 1	291078 40	56998	It seems that the aberrant activation of Wnt/β-catenin signaling in the secretory phase of the menstrual cycle in endometriosis has two essential elements: excessive inactivation of GSK-3β and suppression of the expression of Wnt

					signaling inhibitor DKK-1
48	ADA	adenosine deaminase	29194839	100	The ectoenzymes ADA and ENPP1 are biomarker candidates for endometriosis.
49	ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1	29194839	5167	The ectoenzymes ADA and ENPP1 are biomarker candidates for endometriosis.
50	ENPP3	ectonucleotide pyrophosphatase/phosphodiesterase 3	29194839	5169	The ectoenzymes ADA and ENPP1 are biomarker candidates for endometriosis.
51	miR23b	microRNA 23b	29093245	407011	MiR23b and Sp1 are involved in the pathogenesis of ovarian endometriosis, which may facilitate the formation of ectopic lesions.
52	Sp1	Sp1 transcription factor	29093245	6667	MiR23b and Sp1 are involved in the pathogenesis of ovarian endometriosis, which may facilitate the formation of ectopic lesions.
53	LYN	LYN proto-oncogene, Src family tyrosine kinase	29050963	4067	helps to understand the possibility of using GlcCer to modulate the SDF-1α-CXCR4-LYNpTyr396 axis in endometriosis.
54	GCS	glutamate-cysteine ligase catalytic subunit	29050963	2729	helps to understand the possibility of using GlcCer to modulate the SDF-1α-CXCR4-LYNpTyr396 axis in endometriosis.
55	CXCR4	C-X-C motif chemokine receptor 4	29050963	7852	helps to understand the possibility of using GlcCer to modulate the

					SDF-1α-CXCR4-LYNpTyr396 axis in endometriosis. ignificant elevation of TNF-α, IL-1β and IL-6, significant up-regulation of microRNA 125b and significant down-regulation of Let-7b in sera of endometriosis patients versus control. There was a positive correlation between miR 125b levels and TNF-α, IL-1β, and IL-6 and a negative correlation between miR Let7b levels and TNF-α in sera of patients
56	TNF	tumor necrosis factor	29040578	7124	with endometriosis. ignificant elevation of TNF-α, IL-1β and IL-6, significant up-regulation of microRNA 125b and significant down-regulation of Let-7b in sera of endometriosis patients versus control. There was a positive correlation between miR 125b levels and TNF-α, IL-1β, and IL-6 and a negative correlation between miR Let7b levels and TNF-α in sera of patients
57	IL6	interleukin 6	29040578	3569	with endometriosis. ignificant elevation of TNF-α, IL-1β and IL-6, significant up-regulation of microRNA 125b and
58	IL8	C-X-C motif chemokine ligand 8	29040578	3576	

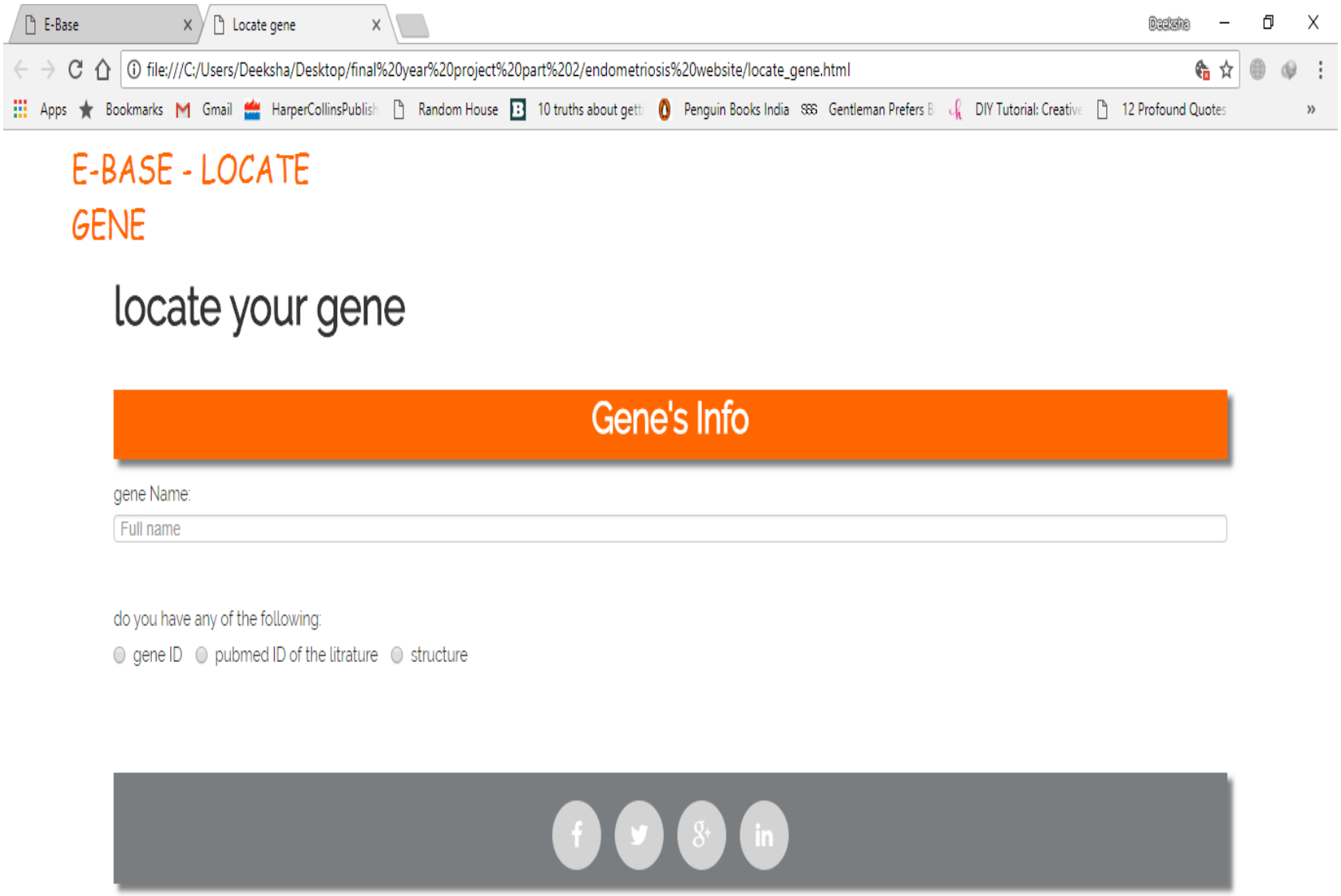
					significant down-regulation of Let-7b in sera of endometriosis patient s versus control. There was a positive correlation between miR 125b levels and TNF-α, IL-1β, and IL-6 and a negative correlation between miR Let7b levels and TNF-α in sera of patients with endometriosis.
59	EDN1	endothelin 1	29034546	1906	blocking endothelin-1 was effective to decrease pain
60	BDKRB2	bradykinin receptor B2	29034546	624	the presence and the function of the BK system in endometriosis
61	CDKN1B	cyclin dependent kinase inhibitor 1B	29216564	1027	endometriosis mainly correlating the cytokine p27kip1 expression with the diagnostic and disease treatment.
62	MIR30C1	microRNA 30c-1	29201189	407031	study indicated that miR-30c serves an important role in the development and progression of EMs by regulating the expression of PAI-1
63	SERPINE1	serpin family E member 1	29201189	5054	study indicated that miR-30c serves an important role in the development and progression of EMs by regulating the expression of PAI-2
64	P2rx3	purinergic receptor P2X 3	29184406	81739	CSOSA/NLC/A-317491 could be used as an effective treatment strategy for P2X3-

					targeted therapy in endometriosis pain. CSOSA/NLC/A-317491 could be used as an effective treatment strategy for P2X3-
65	ccpA	LacI family transcriptional regulator	29184406	5184355	targeted therapy in endometriosis pain.
66	PRDX2	peroxiredoxin 2	29157123	7001	results suggest that upregulation of NAG-1 contributes to TSA-induced apoptosis in HESCs.
67	GDF15	growth differentiation factor 15	29157123	9518	results suggest that upregulation of NAG-1 contributes to TSA-induced apoptosis in HESCs.
68	BECN1	Beclin1	29063947	8678	RA treatment induces autophagy and Beclin1 may play an important role in endometriosis progression
69	RARA	retinoic acid receptor alpha	29063947	5914	RA treatment induces autophagy and Beclin1 may play an important role in endometriosis progression
70	HOXA9	homeobox A9	29017417	3205	the study findings suggest that HOXA11-AS1 lncRNA may play a role in the development of peritoneal endometriosis, but HOXA11-AS1 may not influence endometrial receptivity in endometriosis-associated infertility.
71	HOXA10	homeobox A10	29017417	3206	the study findings suggest that HOXA11-

					AS1 lncRNA may play a role in the development of peritoneal endometriosis , but HOXA11-AS1 may not influence endometrial receptivity in endometriosis-associated infertility. the study findings suggest that HOXA11-AS1 lncRNA may play a role in the development of peritoneal endometriosis , but HOXA11-AS1 may not influence endometrial receptivity in endometriosis-associated infertility. the study findings suggest that HOXA11-AS1 lncRNA may play a role in the development of peritoneal endometriosis , but HOXA11-AS1 may not influence endometrial receptivity in endometriosis-associated infertility. EnSCs proliferation by targeting the 3' untranslated region of VEGFA. miR-34a-5p provides a novel avenue for the understanding of the development of endometriosis the present results suggest that the CFTR-NFκB-uPAR signaling may contribute to the
72	HOXA11-AS	HOXA11 antisense RNA	29017417	221883	
73	HOXA13	homeobox A13	29017417	3209	
74	VEGFA	vascular endothelial growth factor A	28990049	7422	
75	CFTR	cystic fibrosis transmembrane conductance regulator	28978008	1080	

					progression of human endometriosis the present results suggest that the CFTR-NFκB-uPAR signaling may contribute to the progression of human endometriosis
76	PLAUR	plasminogen activator, urokinase receptor	28978008	5329	the present results suggest that the CFTR-NFκB-uPAR signaling may contribute to the progression of human endometriosis
77	KCNE1	potassium voltage-gated channel subfamily E regulatory subunit 1	28978008	3753	the present results suggest that the CFTR-NFκB-uPAR signaling may contribute to the progression of human endometriosis
78	NFKB1	nuclear factor kappa B subunit 1	28978008	4790	study showed for the first time that MFG-E8 expression is impaired in the endometrium of patients with endometriosis
79	MFGE8	milk fat globule-EGF factor 8 protein	28967712	4240	study showed for the first time that MFG-E8 expression is impaired in the endometrium of patients with endometriosis
80	LIF	interleukin 6 family cytokine	28967712	3976	

The screen shots of the web repository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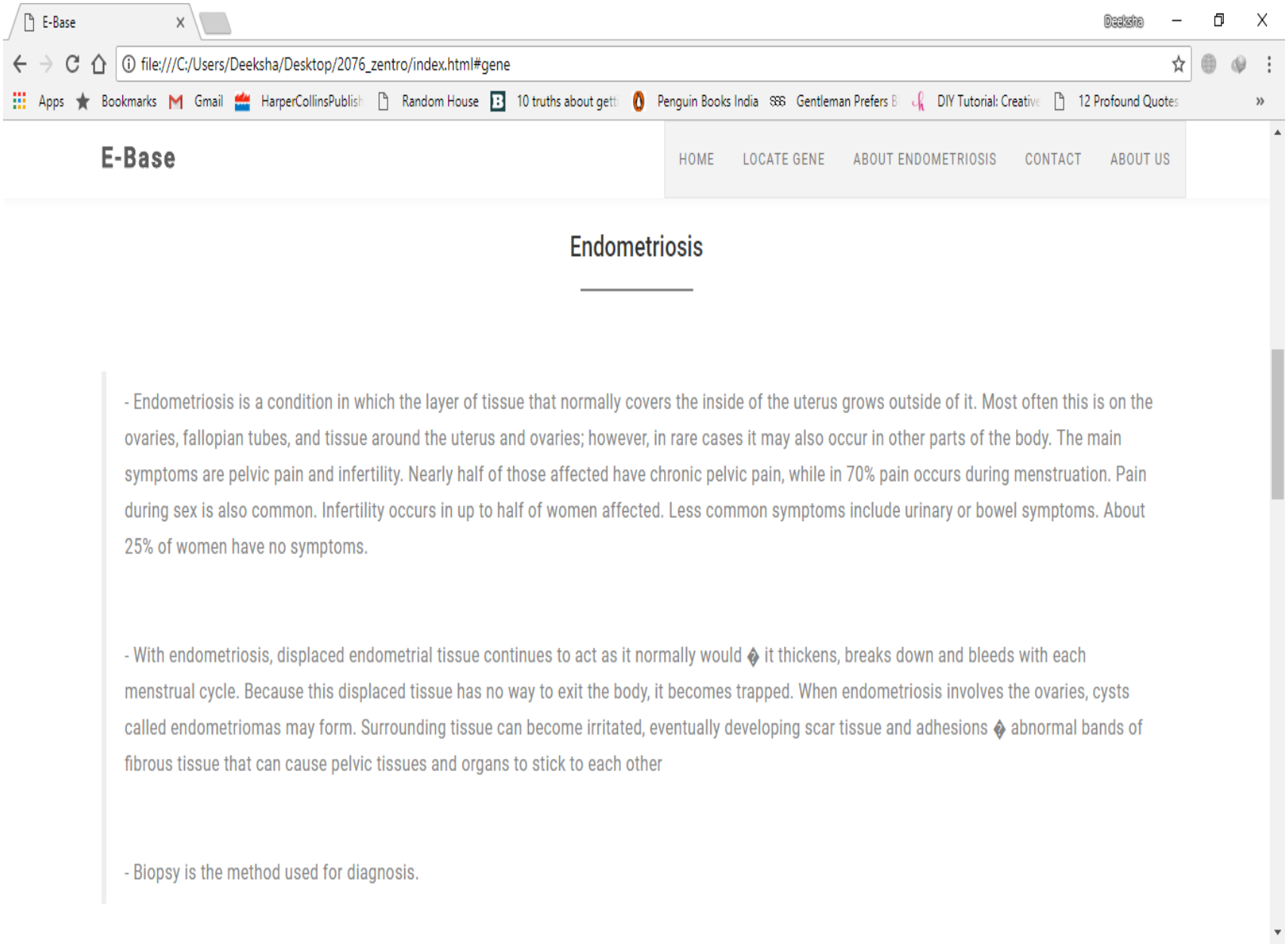
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ABOUT ENDOMETRIOSIS
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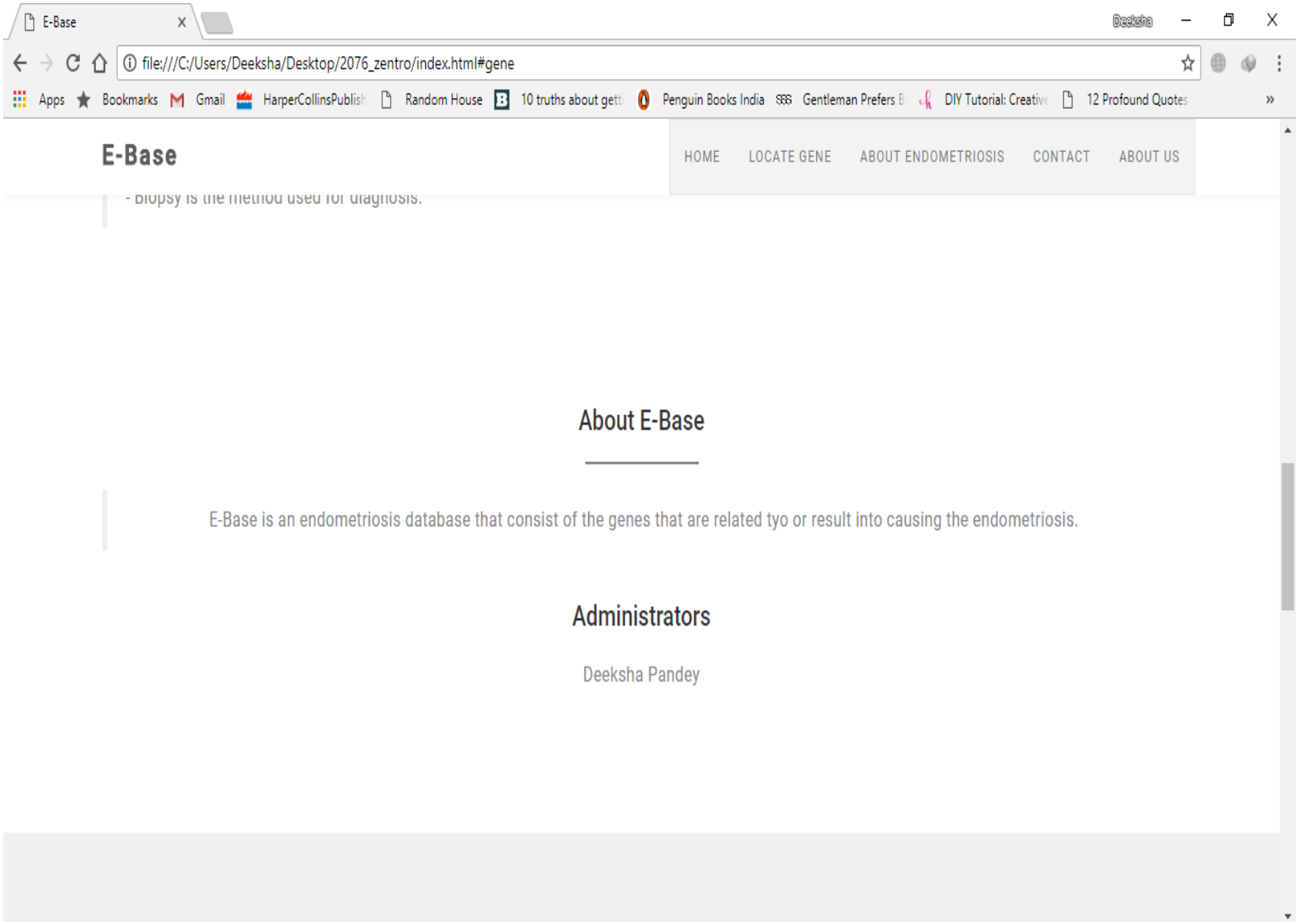
Endometriosis
- Endometriosis is a condition in which the layer of tissue that normally covers the inside of the uterus grows outside of it. Most often this is on the ovaries, fallopian tubes, and tissue around the uterus and ovaries; however, in rare cases it may also occur in other parts of the body. The main symptoms are pelvic pain and infertility. Nearly half of those affected have chronic pelvic pain, while in 70% pain occurs during menstruation. Pain during sex is also common. Infertility occurs in up to half of women affected. Less common symptoms include urinary or bowel symptoms. About 25% of women have no symptoms.
- With endometriosis, displaced endometrial tissue continues to act as it normally would it thickens, breaks down and bleeds with each menstrual cycle. Because this displaced tissue has no way to exit the body, it becomes trapped. When endometriosis involves the ovaries, cysts called endometriomas may form. Surrounding tissue can become irritated, eventually developing scar tissue and adhesions abnormal bands of fibrous tissue that can cause pelvic tissues and organs to stick to each other
- Biopsy is the method used for diagnosis.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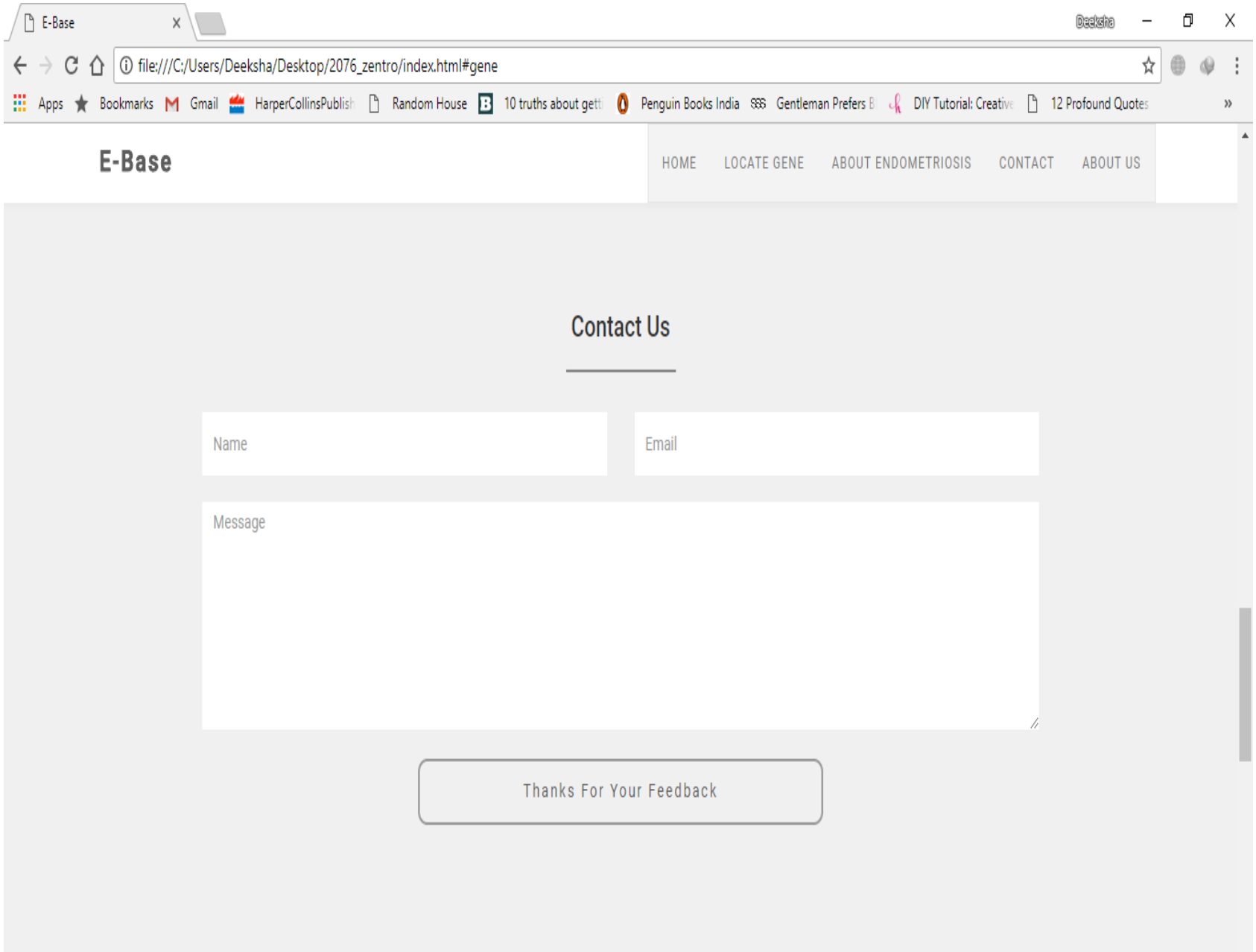
- Biopsy is the method used for diagnosis.
About E-Base
E-Base is an endometriosis database that consist of the genes that are related tyo or result into causing the endometriosis.
Administrators
Deeksha Pandey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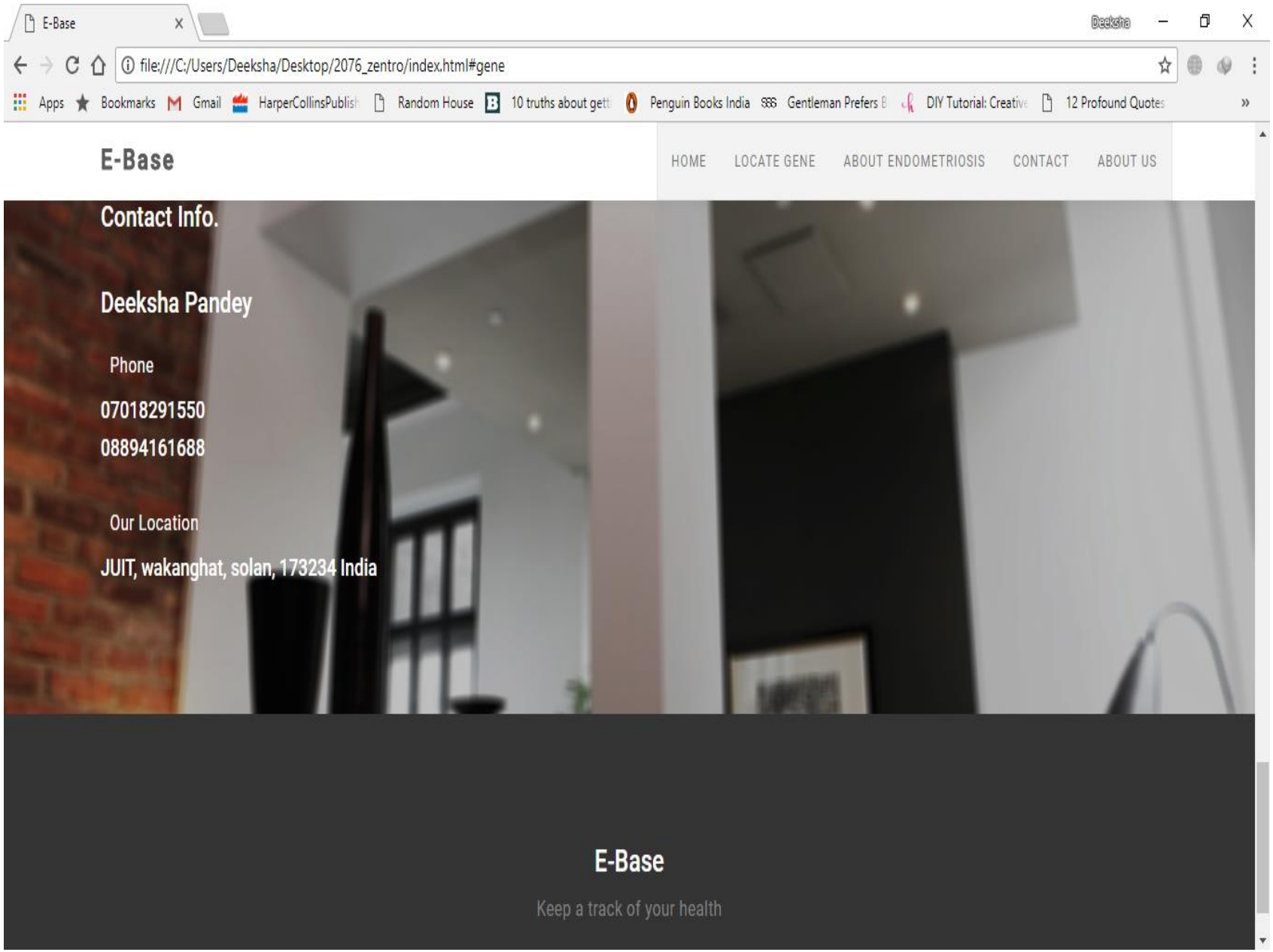
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CONCLUSION

A web resource with a repository of genes was created, this repository consists the genes, their official name, the pubmed id of the research paper they are taken from and their functions in respect to endometriosis.

These gene can be accessed by their official name, pubmed id and structure for further research work conducted by any research fellow, it'll be able to help them with all the basic data and knowledge due to which the research can be taken further without wasting time on collecting the basic data.

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